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FOOD & DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PULMONARY-ALLERGY DRUGS

ADVISORY COMMITTEE (PADAC)

Olodaterol

NDA 203108

Tuesday, January 29, 2013

The Great Room

White Oak Conference Center

White Oak Campus, Building 31

10903 New Hampshire Avenue

Silver Spring, MD 20993

Reported by: Natalia Thomas

Capital Reporting Company

1   Meeting Roster

2   DESIGNATED FEDERAL OFFICER (Non-Voting)

3

4 Cindy Hong, PharmD

5 Division of Advisory Committee and Consultant

6 Management

7 Office of Executive Programs, CDER, FDA

8

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10   (Voting)

11

12 Kathryn Blake, PhD

13 Senior Research Scientist

14 Nemours Children's Clinic

15 Jacksonville, Florida

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17 Paul A. Greenberger, MD

18 Professor of Medicine, Department of Medicine

19 Division of Allergy-Immunology

20 Northwestern University Feinberg School of Medicine

21 Chicago, Illinois

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1   Meeting Roster

2   (continued)

3   PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

4   (Voting) (cont.)

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6 David B. Jacoby, MD

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8 Professor of Medicine

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13 Rodney Mullins

14 (Consumer Representative)

15 National Director, Public Health Consultants

16 and Advocates

17 Duluth, Georgia

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22

1   Meeting Roster

2   (continued)

3   PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

4   (Voting) (cont.)

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6 Kelly Dean Stone, MD, PhD

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15 Johns Hopkins University School of Medicine

16 Baltimore, Maryland

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 1                    Meeting Roster

 2                      (continued)

 3    PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

 4                      (Non-Voting)

 5

 6  Howard M. Druce, MD

 7  (Industry Representative)

 8  Clinical Professor of Medicine

 9  Division of Allergy & Immunology

10  UMDNJ - University of Medicine and Dentistry

11  of New Jersey

12  New Jersey Medical School, Newark, New Jersey

13  Allergy and Immunology, Ear, Nose & Throat Care PC

14  & Allergy

15  Somerville, New Jersey

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1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)

4

5 Bill T. Ameredes, PhD

6 Associate Professor of Medicine

7 Associate Professor of Preventive Medicine and

8 Community Health

9 Director, NIEHS Environmental Toxicology

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14 University of Texas Medical Branch

15 Galveston, Texas

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 1                    Meeting Roster

 2                      (continued)

 3           TEMPORARY MEMBERS (Voting)(cont.)

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 5  Mark Brantly, MD

 6  Chief, Division of Pulmonary, Critical Care and

 7  Sleep Medicine

 8  Professor of Medicine, Molecular Genetics and

 9  Microbiology

10  Alpha One Foundation Research Professor

11  University of Florida College of Medicine

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14  William J. Calhoun, MD

15  Renfert Professor and Vice Chair for Research

16  Department of Internal Medicine

17  University of Texas Medical Branch

18  Galveston, Texas

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1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)(cont.)

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5 Paula G. Carvalho, MD

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12 Boise, Idaho

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14 John E. Connett, PhD

15 Professor

16 Division of Biostatistics

17 School of Public Health

18 University of Minnesota

19 Minneapolis, Minnesota

20

21

22

 1   Meeting Roster

 2   (continued)

 3   TEMPORARY MEMBERS (Voting)(cont.)

 4

 5 Edna Fiore

 6 (Patient Representative)

 7 Littleton, Colorado

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10 Associate Professor of Medicine

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12 and Critical Care Division

13 University of New Mexico

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16 Amy H. Herring, ScD

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18 Department of Biostatistics

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21 Chapel Hill, North Carolina

22

1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)(cont.)

4

5 John Hoidal, MD

6 Professor and Chair of Medicine

7 Professor of Pediatrics

8 Department of Internal Medicine

9 University of Utah

10 Salt Lake City, Utah

11

12 Udho Thadani, MD, MRCP, FRCPC, FACC, FAHA

13 Professor Emeritus of Medicine

14 Division of Cardiology

15 Oklahoma University Medical Center and

16 Oklahoma Veterans Affairs Medical Center

17 Oklahoma City, Oklahoma

18

19

20

21

22

1   Meeting Roster

2   (continued)

3   TEMPORARY MEMBERS (Voting)(cont.)

4

5 James M. Tracy, DO

6 Assistance Clinical Professor of Internal Medicine

7 Creighton University School of Medicine

8 Managing Partner

9 Allergy Asthma & Immunology Associates, P.C.

10 Omaha, Nebraska

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12   FDA MEMBERS (Non-Voting)

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14 Curtis Rosebraugh, MD, MPH

15 Director

16 Office of Drug Evaluation II (ODE-II)

17 Office of New Drugs (OND), CDER, FDA

18

19

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21

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12

1   Meeting Roster

2   (continued)

3   FDA MEMBERS (Non-Voting)(cont.)

4

5 Badrul Chowdhury, MD, PhD

6 Director

7 Division of Pulmonary, Allergy, and

8 Rheumatology Products (DPARP)

9 ODE-II, OND, CDER, FDA

10

11 Theresa Michele, MD

12 Clinical Team Leader

13 DPARP, ODE-II, OND, CDER

14

15 Robert Lim, MD

16 Clinical Reviewer

17 DPARP, ODE-II, OND, CDER

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19

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13

1   Meeting Roster

2   (continued)

3   FDA MEMBERS (Non-Voting)(cont.)

4

5 Robert Abugov, PhD

6 Statistical Reviewer

7 Division of Biostatistics II

8 Office of Biostatistics

9 Office of Translational Sciences, CDER, FDA

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1   P R O C E E D I N G S

2   Call to Order and Introduction of Committee

3   DR. JACOBY: Good morning everyone. If

4   everyone could please take their seats, we can get

5   started. I'd like to remind everyone present to please

6   silence your cell phones, Blackberries, as well as

7   other devices if you haven't already done so.

8   I'd also like to identify the FDA press

9   contact, Mr. Chris Kelly. Mr. Kelly? My name is David

10   Jacoby, I'm the Chair for the Pulmonary Allergy Drug

11   Advisory Committee. I'll now call this meeting of the

12   Pulmonary Allergy Drugs Advisory Committee to order.

13   We'll start by going around the table and introducing

14   ourselves, starting down on the right.

15   DR. DRUCE: Good morning, my name is Howard

16   Druce. I am Clinical Professor of Medicine at the New

17   Jersey Medical School in Newark, New Jersey, and in

18   private practice in allergy and immunology in

19   Somerville, New Jersey.

20   DR. HOIDAL: My name is John Hoidal. I'm a

21   professor at the University of Utah.

22   DR. CARVALHO: Paula Carvalho, Professor of

1 Medicine, University of Washington.

2   DR. THADANI: Udho Thadani, University of

3 Oklahoma, Health Science Center, Professor Emeritus of

4 Medicine and VA Medical Center, Oklahoma City,

5 cardiology.

6   MS. FIORE: Edna Fiore, a patient

7 representative and lung health advocate.

8   DR. HARKINS: Michelle Harkins, Associate

9 Professor of Medicine, University of New Mexico.

10   DR. BLAKE: Kathryn Blake, Senior Research

11 Scientist in the Center for Pharmacogenomics and

12 Translational Research at Nemours Children's Clinic in

13 Jacksonville, Florida.

14   DR. JACOBY: I'm David Jacoby, Professor of

15 Medicine at Oregon Health and Science University.

16   DR. HONG: I'm Cindy Hong, I'm the Designated

17 Federal Officer for the Pulmonary Allergy Drugs

18 Advisory Committee.

19   DR. TERRY: I'm Peter Terry, Professor of

20 Medicine, Johns Hopkins.

21   DR. GREENBERGER: Paul Greenberger, Professor

22 of Medicine, Division of Allergy-Immunology,

1 Northwestern University in Chicago.

2   DR. STONE: Kelly Stone. I'm from the

3 Laboratory of Allergic Diseases, NIAID.

4   DR. TRACY: I'm Jim Tracy, Associate

5 Professor of Medicine at Creighton University and

6 private practice.

7   DR. HERRING: Amy Herring, Professor of

8 Biostatistics at the University of North Carolina at

9 Chapel Hill.

10   DR. BRANTLY: Mark Brantly, Professor of

11 Medicine at the University of Florida.

12   DR. ABUGOV: Robert Abugov, Statistical

13 Reviewer for the FDA.

14   DR. LIM: Robert Lim, Medical Officer, FDA.

15   DR. MICHELE: Terri Michele, Clinical Team

16 Leader, Division of Pulmonary, Allergy and Rheumatology

17 Products at FDA.

18   DR. CHOWDHURY: I'm Badrul Chowdhury,

19 Division Director, Division of Pulmonary, Allergy and

20 Rheumatology Products, FDA.

21   DR. ROSEBRAUGH: Curt Rosebraugh, Office

22 Director, ODE-II.

1   DR. JACOBY: Thank you. For topics such as

2 those being discussed at today's meeting, there are

3 often a variety of opinions, some of which are quite

4 strongly held. Our goal is that today's meeting will

5 be a fair and open forum for discussion of these

6 issues, and that individuals can express their views

7 without interruption. Thus, as a gentle reminder,

8 individuals will be allowed to speak into the record

9 only if recognized by the chair. We look forward to a

10 productive meeting.

11   In the spirit of the Federal Advisory

12 Committee Act and the Government in the Sunshine Act,

13 we ask that the advisory committee members take care

14 that their conversations about the topic at hand take

15 place in the open forum of the meeting. We're aware

16 that members of the media are anxious to speak with the

17 FDA about the proceedings, however FDA will refrain

18 from discussing the details of this meeting with the

19 media until its conclusion. Also the committee is

20 reminded to please refrain from discussing the meeting

21 topic during breaks or lunch. Thank you. Conflict of

22 Interest

24

1   DR. HONG: The Food and Drug Administration

2   is convening today's meeting of the Pulmonary Allergy

3   Drugs Advisory Committee under the authority of the

4   Federal Advisory Committee Act of 1972. With the

5   exception of industry representative, all members and

6   temporary members of the committee are special

7   government employees, or regular federal employees from

8   other agencies and are subject to federal conflicts of

9   interest laws and regulations.

10   The following information on the status of

11   this committee's compliance with federal ethics and

12   conflict of interest laws, covered by but not limited

13   to those found at 18 USC, Section 208, is being

14   provided to participants in today's meeting and to the

15   public.

16   FDA has determined that members and temporary

17   voting members of this committee are in compliance with

18   federal ethics and conflict of interest laws. Under 18

19   USC, Section 208, Congress has authorized FDA to grant

20   waivers to special government employees and regular

21   federal employees who have potential financial

22   conflicts when it is determined that the agency's need

1 for a particular individual's service outweighs his or

2 her potential financial conflict of interest.

3   Related to the discussion of today's meeting,

4 members and temporary voting members of this committee

5 have been screened for potential financial conflicts of

6 interest of their own, as well as those imputed to

7 them, including those of their spouses or minor

8 children, and for purposes of 18 USC, Section 208,

9 their employers. These interests may include

10 investments, consulting, expert witness testimony,

11 contracts, grants, CRADAs, teaching, speaking, writing,

12 patents and royalties, and primary employment.

13   Today's agenda involves discussion of new

14 drug application 203108 for olodaterol, proposed trade

15 name Striverdi Respimat, metered dose inhaler,

16 sponsored by Boehringer Ingelheim, for the proposed

17 indication of long-term, once-daily maintenance

18 bronchodilator treatment of airflow obstruction in

19 patients with chronic obstructive pulmonary disease,

20 including chronic bronchitis and/or emphysema. This is

21 a meeting during which specific matters related

22 to Boehringer Ingelheim's olodaterol will be

1 discussed.

2   Based on the agenda and all financial

3 interests reported by the committee members and

4 temporary voting members, no conflict of interest

5 waivers have been issued in connection with this

6 session. To ensure transparency, we encourage all

7 standing committee members and temporary voting members

8 to disclose any public statements that they have made

9 concerning the product at issue.

10   With respect to FDA's invited industry

11 representative, we would like to disclose that Dr.

12 Howard Druce is participating in this meeting as a non-

13 voting industry representative, acting on behalf of

14 regulated industry. Dr. Druce's role at this meeting

15 is to represent industry in general and not any

16 particular company. Dr. Druce is an independent

17 pharmaceutical industry consultant.

18   We would like to remind members and temporary

19 members that if the discussions involve any other

20 products or firms not already on the agenda for which

21 an FDA participant has a personal or imputed financial

22 interest, the participants need to exclude themselves

1 from such involvement and their exclusion will be noted

2 for the record. FDA encourages all other participants

3 to advise the committee of any financial relationships

4 that they may have with the firm at issue. Thank you.

5   DR. JACOBY: We'll now proceed with the

6 FDA opening remarks from Dr. Theresa Michele. I'd like

7 to remind public observers at this meeting that while

8 this meeting is open for public observation, public

9 attendees may not participant except at the specific

10 request of the panel. Opening Remarks

11   DR. MICHELE: Good morning, Dr. Jacoby,

12 members of the Pulmonary Allergy Drugs Advisory

13 Committee, representatives from Boehringer Ingelheim,

14 and members of the public. On behalf of the FDA, it is

15 my pleasure to welcome you to the FDA campus at White

16 Oak.

17   Today we are here to discuss the new drug

18 application for olodaterol for the treatment of chronic

19 obstructive pulmonary disease, or COPD, a progressive

20 lung disease that sadly is now the third leading cause

21 of death in the United States.

22   Before we get started, I would like to thank

1 the members of the advisory committee who have taken

2 time out of their busy schedules to thoughtfully review

3 the briefing package and to be here today. As members

4 of the scientific advisory committee, you provide

5 important expert advice that is taken very seriously by

6 the FDA.

7   Olodaterol, trade name Striverdi Respimat, is

8 a new molecular entity that belongs to the class of

9 long- acting beta agonists. U.S. marketed products in

10 this class include salmeterol, formoterol and

11 indacaterol.

12   Olodaterol is formulated as an inhalation

13 solution delivered via the Respimat device. The

14 Respimat device is relatively new to the U.S. market,

15 with the first U.S. approval as Combivent Respimat just

16 over a year ago in October 2011. The Respimat device

17 has no propellants and uses a spring mechanism to

18 release the medication.

19   The proposed indication for olodaterol is for

20 the long-term, once-daily maintenance bronchodilator

21 treatment of airflow obstruction in patients with

22 chronic obstructive pulmonary disease, or COPD,

1 including chronic bronchitis and emphysema.

2   This indication for COPD is consistent with

3 the indication of other single-agent products in the

4 LABA class. Unlike salmeterol and formoterol, the

5 sponsor is not proposing an asthma indication for

6 olodaterol, although you will see asthma dose ranging

7 studies in the clinical program that were requested by

8 FDA to better define the dose and dosing regimen in a

9 more bronchoresponsive population. The proposed dose

10 of olodaterol is 5 micrograms once-daily.

11   The topics for discussion today will be the

12 safety and efficacy of olodaterol. Under efficacy

13 there are two areas to discuss. First, the

14 bronchodilator claim is the primary indication for

15 olodaterol, which as I mentioned, is standard for

16 agents of this class.

17   Secondly, Boehringer Ingelheim is requesting

18 a claim that olodaterol improves exercise endurance

19 time and increases inspiratory capacity, indicative of

20 a reduction in hyperinflation. If approved, olodaterol

21 would be the first COPD product to have such a claim.

22 Thus a regulatory pathway for these claims is not

1 established.

2   FDA recognizes measurement of exercise

3 capacity by cycle ergometry, combined with lung volume

4 measurement assessing dynamic hyperinflation, as a

5 valid, objective endpoint that could measure

6 improvement in airflow obstruction in COPD patients.

7 However, exactly how to operationalize this in a

8 clinical trial, and what constitutes a clinically

9 meaningful improvement on these endpoints, remains to

10 be determined. Therefore, we are particularly looking

11 for your input and expertise on this topic.

12   Boehringer Ingelheim performed an extensive

13 development program for olodaterol consisting of seven

14 dose ranging and dose regimen trials, three of which

15 were in COPD, and four in asthma, four 48-week trials

16 and six six-week trials, two of which were focused on

17 exercise. All of the trials included both a 5 microgram

18 and a 10 microgram olodaterol dose, providing

19 additional dose ranging data from Phase III.

20   The majority of the trials permitted usual

21 care background therapy, including tiotropium, but

22 excluded the use of LABAs. Given the known dose-

1 related class effects of LABAs, including both serious

2 respiratory events and cardiovascular events, including

3 tachycardia, FDA takes dose ranging for these products

4 very seriously.

5   For olodaterol, the sponsor performed an

6 extensive dose ranging program in both asthma and COPD,

7 as well as providing additional dose ranging in Phase

8 III. Dr. Lim will summarize the dose ranging data

9 briefly, and the data are also available to you in your

10 background package. However, since FDA is in agreement

11 with the sponsor regarding dose selection, we do not

12 intend to focus on the dose ranging trials during this

13 meeting.

14   Instead, the majority of the discussion will

15 focus on the 48-week trials, as these form the basis of

16 both the primary efficacy claim and the primary safety

17 database. In addition, we will cover the exercise

18 trials since we would like for you to provide input

19 regarding the trial design and how to interpret the

20 data.

21   The primary efficacy and safety trials for

22 this application consisted of four 48-week parallel

1 group spirometry trials in patients with moderate to

2 severe COPD. All trials included olodaterol 5

3 micrograms, olodaterol 10 micrograms, and placebo arms.

4 Two of the trials also included the active comparator

5 formoterol, using the European formulation of Foradil.

6 Inclusion of an active comparator arm in pivotal trials

7 is generally required for approval in the European

8 Union.

9   While all trials included trough FEV1 and

10 FEV1 AUC zero to three hours as primary endpoints, the

11 primary endpoints were defined to be at 12 weeks for

12 the first two trials, which is standard for U.S.

13 approval, and at 24 weeks in the other two trials,

14 which is the standard for European approval. For ease

15 of comparison between trials, the majority of FDA

16 presentations will show the 12-week endpoints for all

17 the trials.

18   To support the exercise claim, the sponsor

19 performed two identically designed six-week exercise

20 trials in patients with moderate to severe COPD. These

21 trials were three-way crossover trials including

22 olodaterol 5 micrograms, olodaterol 10 micrograms, and

1 placebo. The primary endpoint was exercise endurance

2 time during constant rate cycle ergometry to symptom

3 limitation at 75 percent maximum work capacity.

4 Inspiratory capacity during exercise was a key

5 secondary endpoint.

6   Before I close, I just wanted to mention the

7 legal framework that gives the FDA the ability to hold

8 advisory committees to ask for scientific advice and

9 recommendations from experts in the field. As I noted

10 previously, the FDA takes very seriously the advice of

11 the committee. However, the Commissioner has sole

12 discretion on actions taken with regard to drug

13 approval, especially since there may be other issues,

14 such as manufacturing, not discussed at the meeting,

15 that impact approval decisions.

16   At this point, I would once again like to

17 thank the committee for your input and for sharing your

18 scientific expertise and I will turn the podium over to

19 Boehringer Ingelheim for their presentations. Thank

20 you.

21   DR. JACOBY: Thank you, Dr. Michele. Before

22 we go on, could I ask Dr. Calhoun and Dr. Connett to

1 please introduce themselves, and Dr. Ameredes?

2   DR. CALHOUN: Pardon me for being late. I'm

3 Bill Calhoun. I'm a Professor of Medicine, Vice Chair

4 for Research in the Department of Medicine at the

5 University of Texas Medical Branch in Galveston. My

6 training is in pulmonary critical care and allergy and

7 immunology.

8   DR. AMEREDES: Hi, I'm Bill Ameredes. Sorry

9 we're late today. I'm from the University of Texas

10 Medical Branch. I'm a respiratory physiologist by

11 training. I'm Associate Professor of Medicine in the

12 Pulmonary, Allergy and Critical Care Medicine Division.

13   DR. CONNETT: I'm John Connett. I am

14 Professor of Biostatistics at the University of

15 Minnesota.

16   DR. JACOBY: Thank You. We'll now proceed

17 with the sponsor presentations. Both the Food and Drug

18 Administration and the public believe in a transparent

19 process for information gathering and decision making.

20 To ensure such transparency at the advisory committee

21 meeting, FDA believes it is important to understand the

22 context of an individual's presentation.

1   For this reason FDA encourages all

2 participants, including sponsor's non-employee

3 presenters, to advise the committee of any financial

4 relationships that they may have with the firm at

5 issue, such as consulting fees, travel expense,

6 honoraria and interests in the sponsor, including

7 equity interests and those based upon the outcome of

8 the meeting.

9   Likewise, FDA encourages you, at the

10 beginning of your presentation, to advise the committee

11 if you do not have any such financial relationships.

12 If you choose not to address the issue of financial

13 relationships at the beginning of your presentation, it

14 will not preclude from speaking. Sponsor Presentations

15 Introduction

16   DR. LUIK: Good morning, members of the

17 Pulmonary Allergy Drugs Advisory Committee, FDA

18 representatives, and members of the audience. My name

19 is Sabine Luik. I am Head of U.S. Medicine and

20 Regulatory Affairs for Boehringer Ingelheim

21 Pharmaceuticals Incorporated. On behalf of Boehringer

22 Ingelheim, I'd like to thank you for the opportunity to

1 discuss our development program for olodaterol in COPD.

2   Olodaterol Respimat inhalation spray is the

3 most recent therapy Boehringer Ingelheim has developed

4 for COPD. The proposed trade name for olodaterol

5 Respimat is Striverdi Respimat. Olodaterol is a highly

6 selective, a long-acting beta2-agonist with physical,

7 chemical and pharmacodynamic features that make it an

8 ideal candidate for once-daily dosing.

9   Olodaterol has been developed using the

10 Respimat inhaler. This is a metered dose inhalation

11 spray device that uses mechanical energy, not

12 propellants, to deliver a slow-moving aerosol mist of

13 medication to the patient. Each Respimat provides 30

14 days of dosing. The Respimat device is already

15 approved for use in the United States with a short-

16 acting ipratropium and albuterol inhalation spray

17 combination drug product, Combivent Respimat.

18   Important aspects to know today are the

19 following. Olodaterol Respimat has been developed

20 according to global requirements, and the clinical

21 development reflects feedback from regulatory

22 authorities, including the FDA.

 1   The patient population enrolled in the

 2 studies was representative of the overall COPD

 3 population requiring maintenance therapy. Patients in

 4 the 48-week trials were allowed to continue on their

 5 usual care, therefore when we discuss placebo patients

 6 in our 48-week studies, we are actually discussing

 7 patients who continued on background treatment plus

 8 placebo.

 9   Overall, 28 studies make up the clinical

10 program for olodaterol, 4,239 COPD patients in Phase II

11 and III, 731 patients with asthma, and 276 healthy

12 volunteers.

13   The Phase III program for olodaterol Respimat

14 includes 10 studies: two pairs of pivotal 48-week

15 studies, two pairs of six-week bronchodilator profile

16 studies, and one pair of exercise tolerance studies.

17 The Phase III studies also provide evidence of benefit

18 in patient relevant outcomes, such as shortness of

19 breath and reduction in rescue medication use. We will

20 review the Phase III program in great detail in a

21 subsequent presentation.

22   In the course of our presentation today, you

1 will see that the olodaterol development program

2 supports the following conclusions. Olodaterol 5

3 microgram once- daily improved lung function compared

4 to placebo over one year in patients with moderate to

5 very severe COPD. Lung function improvements were

6 evident in all patient subgroups. The lung function

7 improvements were in line with expectations when

8 considering the population studied and the background

9 therapies allowed.

10   Olodaterol had a rapid onset of action,

11 comparable to formoterol, evident five minutes post-

12 dose. Olodaterol improved exercise tolerance versus

13 placebo. And finally, the safety profile was consistent

14 with other LABAs with no new major safety concerns

15 identified among any patient subgroup or co-medication

16 subgroup.

17   We conclude that these data support the

18 approval of olodaterol Respimat 5 microgram as an

19 inhalation therapy indicated for long-term, once-daily

20 maintenance bronchodilator treatment of airflow

21 obstruction in patients with COPD, including chronic

22 bronchitis and/or emphysema.

1   It is important to recognize the limitations

2   to the proposed use of olodaterol Respimat inhalation

3   spray. It is not intended for rescue use or to treat

4   asthma.

5   This morning Dr. Richard Casaburi will

6   provide background information on COPD and the current

7   state of the art in treating patients. Dr. Casaburi is

8   Professor of Medicine at Harbor-UCLA Medical Center, a

9   recognized leader in clinical investigations and COPD

10 in general, and an expert in exercise physiology.

11   Dr. Casaburi's presentation will be followed

12 by a review of the efficacy data supporting our NDA for

13 olodaterol Respimat by Dr. Alan Hamilton. Dr. Hamilton

14 is the global medical lead for the development of

15 olodaterol Respimat.

16   This will be followed by a review of the

17 safety information supporting the positive benefit risk

18 assessment for olodaterol Respimat. This information

19 will be presented by Dr. Bernd Disse, the global

20 therapeutic area head for respiratory medicine at

21 Boehringer Ingelheim.

22   Dr. Casaburi will return to discuss

1 overarching themes in our clinical development program.

2 And in addition, he will be addressing the exercise

3 tolerance data and how this information can inform

4 physicians treating patients with COPD.

5   Dr. Disse will help direct any clarification

6 the advisory committee may have at the end of the

7 presentations. The advisors identified on this slide

8 will be assisting Boehringer Ingelheim in addressing

9 specific questions or clarifications requested by the

10 advisory committee during the meeting today.

11   And now, I'd like to invite Dr. Richard

12 Casaburi to the podium to discuss the current treatment

13 options available for COPD patients. Sponsor COPD

14 Disease Background

15   DR. CASABURI: Good morning. My name is

16 Richard Casaburi. I've been paid as a consultant by

17 Boehringer Ingelheim, and my transportation and lodging

18 have been provided.

19   I'm a pulmonologist and I've been doing COPD

20 research for over 25 years. I direct a laboratory

21 dedicated to improving lives of COPD patients. It's

22 always nice to see a new drug come along, a new drug

1 that has the potential to help COPD patients.

2   There's been a shift in the attitude towards

3 COPD that I've seen in my years in this field. When I

4 started, COPD was considered to be a hopeless, chronic

5 disease, characterized by irreversible airflow

6 limitation, for which no effective therapy was

7 available. Today we feel differently.

8   We view COPD as a preventable, treatable

9 disease. Preventable if people don't smoke, and

10 treatable because we now have drugs that make a

11 difference in their lives. We feel that their airflow

12 limitation is not fully reversible, but does have a

13 reversible component that's important to the patient.

14 International guidelines generally agree with this

15 definition.

16   The other reason why I've been kept busy for

17 the last 25 years is that COPD is a tremendous

18 healthcare burden. About 14 million people in the

19 United States are diagnosed with COPD, and another 12

20 million have COPD but don't know it. COPD has become

21 the third leading cause of death in the United States,

22 and the only one of the top five causes of death for

1 which death rates continue to rise. It's a very heavy

2 burden on the healthcare system, with high number of

3 doctor visits and hospitalizations, and roughly $15

4 billion in total healthcare costs annually.

5   Our idea of what the typical COPD patient

6 looks like has changed. It used to be mostly disease

7 of elderly men, but as of the year 2000, it has killed

8 as many women as men. As you see in the pie chart,

9 COPD is no longer only a disease of the elderly, with

10 the majority of patients under 65 years old.

11   The pathophysiology of COPD involves airflow

12 limitation. The patient has trouble breathing out. We

13 see here why this is so. On the left is a normal lung,

14 where during expiration air is propelled very

15 efficiently out of the lung.

16   Elastic recoil of the alveoli forces air out

17 once they are stretched by inspiration. The airways

18 are widely patent, first of all because there's

19 alveolar support tethering the airways open. The

20 bronchial walls are thin, and there's no bronchial

21 constrictor tone.

22   In the COPD lung, a lot of things go wrong.

1 The lung loses elastic recoil so the force propelling

2 air out of the lung is reduced. There is loss of

3 alveolar tissues, so the airways are not tethered open

4 and tend to collapse as expiratory pressure compresses

5 them.

6   We have inflamed and bronchial constricted

7 airways, this increases airflow resistance. So the

8 lack of tethering and bronchial constriction results in

9 increased airways resistance, yielding expiratory

10 airflow limitation. Air trapping occurs when the

11 patient's unable to get all the air out during the time

12 available for expiration.

13   As a result, we classify COPD severity based

14 on the ability to get air out of the lungs. We

15 quantify this with the FEV1, derived from a forced

16 expiratory maneuver in which a patient takes a deep

17 breath in and then breathes out forcefully. We measure

18 the air expelled in the first second, divided by the

19 total amount of air exhaled.

20   A normal person will exhale roughly 80

21 percent in the first second. If less than 70 percent,

22 we define this as airflow obstruction. Then, based on

1 the percent of the patient's predicted FEV1, we decide

2 how severe the airflow limitation is.

3   These are the global obstructive lung disease

4 guidelines for quantifying FEV1 decrement: mild is

5 greater than the 80 percent predicted; moderate between

6 50 and 80 percent; severe between 30 and 50 percent;

7 and very severe less than 30 percent. This

8 classification is roughly in proportion to the symptoms

9 the patient will experience.

10   As I said, we now have drugs that appreciably

11 reduce airflow obstruction. We see here in a study

12 that determined the amount of FEV1 increase that was

13 seen shortly after a dose of the bronchodilator

14 albuterol. The FEV1 increase has been plotted for

15 groups of moderate, severe and very severe COPD

16 patients, that is GOLD II, III and IV.

17   We can see that FEV1 increases in all groups,

18 although the increase is less as the severity gets

19 greater. However, if this is expressed as a percent

20 increase in FEV1, we see that all groups get between 7

21 and 10 percent improvement in their FEV1. This

22 reversibility is the target for our therapies.

1   We're getting to be, in a sense, a victim of

2 our own success in treating our patients. In the old

3 days, we would enroll patients in long clinical trials

4 and have controls who would receive no maintenance

5 bronchodilator therapy.

6   This slide shows three studies of the

7 response to tiotropium, measuring responses at trough,

8 that is just before the next dose of drug. The two

9 cases on the left hand side are from older studies

10 where neither the tiotropium nor the control group were

11 allowed on other maintenance bronchodilators. We see

12 an increase relative to placebo of 150 milliliters, an

13 increase relative to ipotropium of 180 milliliters.

14   On the right we see a different case. In the

15 later trial, UPLIFT, patients were allowed to be on

16 long- acting maintenance bronchodilator therapy, beta

17 agonist maintenance therapy, and their response to

18 tiotropium was less. The lesson is that when we give a

19 drug on the background of maintenance therapy, we can

20 expect somewhat less response.

21   In summary, COPD patients have important

22 medical needs and bronchodilators are essential to

1 meeting those treatment goals. These goals include

2 improving lung airflow, reducing rescue bronchodilator

3 use, reducing the symptom of dyspnea, improving

4 healthcare related quality of life, and finally

5 improving the ability to exercise.

6   This last goal requires special attention.

7 The FDA briefing document has asked for more

8 explanation of the exercise testing methodology that

9 was used in the olodaterol studies, and I'm pleased to

10 provide an introduction.

11   Exercise intolerance is a special interest of

12 mine. It's one of the key ways in which expiatory

13 airflow limitation is important to the patient. It's

14 been found that even patients with mild COPD

15 demonstrate reduced exercise tolerance. Dyspnea on

16 exertion is often a chief complaint of COPD patients,

17 the thing that limits their life the most. The

18 mechanism for exercise endurance reduction is dynamic

19 hyperinflation, and I'll try to explain how this works.

20   This is a spirogram, the time course of lung

21 volume. Focus on the curve above for a minute. After

22 taking a deep breath in and out, a patient breathes

1 along normally and then starts exercising. When you

2 exercise, you have to breathe more deeply and more

3 rapidly.

4   The healthy subject decreases end-expiratory

5 lung volume and increases end-expiratory lung volume.

6 It goes to very rapid rates and exchanges tremendous

7 amounts of air. And even so, in the healthy subject,

8 breathing never limits exercise tolerance. In the COPD

9 patient, when exercise requires they breathe more

10 deeply and rapidly, a point is reached when they

11 experience intolerable shortness of breath. They

12 breathe in and out, in and out, deeper and faster, but

13 reach a point when breathing out can't be finished

14 before they must breathe in. They can't finish their

15 expiration.

16   The only choice is for end-expiratory lung

17 volume to rise. This is termed dynamic hyperinflation.

18 Eventually the patient reaches a point where their

19 inspiratory lung volume approaches the maximum amount

20 of air they can take in, the total lung capacity. This

21 causes severe dyspnea and the patient must stop

22 exercise. Please note that if we can let the patient

1 breathe out faster, they'll get to a lower lung volume

2 during the breath and lessen dynamic hyperinflation.

3 This is why bronchodilators increase exercise

4 tolerance.

5   We can assess this in the exercise

6 laboratory. We periodically have the patient at end-

7 expiration, take a deep breath in to total lung

8 capacity. This is known as an inspiratory capacity

9 breath. In the healthy subject, inspiratory capacity

10 increases during exercise, telling us that end-

11 expiratory lung volume has decreased. In the COPD

12 patient a falling inspiratory capacity shows that end-

13 expiratory lung volume's increased, in other words that

14 dynamic hyperinflation has occurred.

15   Pulmonary society recommendations, pulmonary

16 society statements, I'm sorry, recommend constant work

17 rate testing to assess response to interventions. This

18 was a test that was used in the olodaterol studies.

19 Constant work rate testing determines how long a task

20 can be sustained. These are the kind of tasks that

21 COPD patients encounter in their everyday life. How

22 far can the patient walk at a given pace? How many

1 stairs can be ascended at a constant rate?

2   Cycle ergometer testing is generally used

3 because it allows precise metering of work rate. The

4 testing methodology involves designing a work rate for

5 each individual that at baseline can be tolerated for a

6 targeted period of time, usually in the range of four

7 to eight minutes. An advantage of this test is that

8 the exercise duration response to an intervention is a

9 more sensitive measure of improvement in exercise

10 capacity than in other tests.

11   Another advantage of the constant work rate

12 test is we can observe isotime responses. Evaluation

13 of measurements at isotime are especially valuable in a

14 crossover study design because they allow us to observe

15 responses to identical exercise tasks, the same work

16 rate, the same duration, before and after an

17 intervention. This allows determination of effort-

18 independent physiologic benefits of a therapy.

19   So here again are the goals of maintenance

20 bronchodilator therapy in COPD. I've tried to set the

21 stage for considering the efficacy data that's been

22 gathered for olodaterol. I now invite Dr. Alan

1 Hamilton to the podium who will present these data.

2 Olodaterol Clinical Program

3   DR. HAMILTON: Thank you, Dr. Casaburi. Good

4 morning, my name is Alan Hamilton, a clinical program

5 leader for olodaterol. This morning I will review the

6 efficacy results from the Phase III studies with

7 olodaterol. I'll start with an inventory of studies

8 conducted within the clinical program, and then briefly

9 describe the main Phase II results that supported the

10 selection of the Phase III doses.

11   The main focus of my presentation will be the

12 Phase III lung function results for olodaterol 5

13 micrograms once-daily. I'll also be sharing some

14 supportive data from a number of symptom-based

15 endpoints. And then the final part of my presentation

16 will focus on our exercise tolerance studies, since

17 these will be a specific discussion topic for the

18 committee today.

19   To begin, I'd like to highlight a few key

20 terms that I will be using during my presentation. The

21 main focus today will be lung function, and I'll be

22 sharing a lot of data on FEV1, AUC 0-3 and trough. Now

1 when describing the AUC data, the area under the curve

2 has been divided by the measurement time period to give

3 the results as a weighted average in liters.

4 Throughout the presentation, trough represents the FEV1

5 at the end of the 24-hour dosing interval, prior to the

6 next morning dose. And this applies to both once and

7 twice-daily dosing.

8   Pretreatment baseline was calculated as the

9 average of two measurements taken at one hour and at

10 ten minutes prior to the first dose of study

11 medication. And finally, much of the data presented

12 today will be shown as FEV1 response, which is the

13 change from pretreatment baseline.

14   In Phase II, we investigated the efficacy of

15 olodaterol in both COPD and asthma with single-dose

16 studies to confirm a 24-hour bronchodilating activity,

17 followed by four-week dose ranging studies using once-

18 daily dosing. On the recommendation of the FDA, we

19 conducted additional studies, in both COPD and asthma,

20 to compare the 24-hour lung function efficacy of

21 olodaterol when administered once or twice daily.

22   The Phase III program in COPD comprised five

1 sets of replicate studies, and I'll discuss these

2 studies in more detail later in my presentation.

3   So let's start with our Phase II studies.

4 The results from the four-week studies in asthma and

5 COPD supported the selection of the Phase III doses.

6 Here we see the primary endpoint of FEV1 area under the

7 curve over 24 hours, in the asthma Study 27. Two

8 micrograms was an effective dose and was on the steep

9 part of the dose response curve. Dose ordering was

10 observed up to 20 micrograms.

11   Now on the right, we see the primary endpoint

12 of trough FEV1 response in the COPD Study 5. Again the

13 2 microgram dose was on the steep part of the dose

14 response curve. At higher doses, there was little

15 benefit observed for 20 micrograms compared to 10

16 micrograms. So based on these data, we selected 5 and

17 10 micrograms for further evaluation in our Phase III

18 studies.

19   So now let's turn our attention to the Phase

20 III program in COPD. After a short overview of the 10

21 studies included in Phase III, I'll focus on the

22 pivotal studies providing some background on the

1 design, inclusion criteria and patient demographics.

2 Then I'll present the lung function efficacy results

3 focusing first on olodaterol 5 micrograms and then

4 comparing with olodaterol 10 micrograms. And to

5 finish, I'll provide some context to the differences in

6 effect size across the various Phase III studies.

7   All studies in Phase III included 5 and 10

8 micrograms once-daily. The core program consisted of

9 four sets of replicate studies. Studies 11, 12, 13 and

10 14 were designated as the pivotal trials evaluating

11 long- term efficacy and safety. 11 and 12 were

12 designed to fulfill U.S. regulatory requirements, while

13 13 and 14 fulfilled European requirements.

14   Nevertheless, at the end of Phase II meeting,

15 we agreed with the FDA that the efficacy evaluation

16 should be based on the totality of evidence from all

17 Phase III studies.

18   All four studies were randomized, double-

19 blind, placebo-controlled, parallel group trials of 48

20 weeks duration. In 13 and 14, twice-daily formoterol

21 was included as an active compactor, according to a

22 double- blind, double-dummy design. All four studies

1 used lung function as the primary efficacy assessment,

2 with measurements pre-dose and up to three hours post-

3 dose. In 13 and 14, the TDI was identified as a co-

4 primary endpoint to assess symptomatic benefit as per

5 European requirements. And the SGRQ was included as a

6 key secondary endpoint to assess health-related quality

7 of life.

8   Beyond the pivotal trials, we conducted two

9 sets of replicate, randomized, placebo-controlled,

10 crossover studies. In these studies, serial spirometry

11 was performed throughout one continuous 24-hour dosing

12 interval after six weeks. Both sets of studies

13 included an active comparator using a double-blind,

14 double-dummy design. 24 and 25 included twice-daily

15 formoterol, while 39 and 40 included once-daily

16 tiotropium HandiHaler.

17   Two additional replicate studies, Studies 37

18 and 38, assessed the effects of olodaterol on exercise

19 tolerance. In these studies, the primary endpoint was

20 in exercise endurance time, during cycle ergometry,

21 with key secondary endpoints of inspiratory capacity

22 and intensity of breathing discomfort during exercise.

1   So now we'll look more closely at the 48-week

2 pivotal trials. Patient eligibility was assessed

3 during an initial screening visit, followed by a two-

4 week run in prior to randomization. After 48 weeks of

5 treatment, patients were followed for an additional two

6 weeks prior to trial completion. Spirometry was

7 performed at each visit, according to ATS-ERS

8 standards. The same spirometry equipment was provided

9 to all sites, and centralized reading was conducted for

10 quality control.

11   Pre-dose spirometry was performed at each

12 visit, as shown by the blue circles, while post-dose

13 spirometry was performed at selective visits, as shown

14 by the orange squares.

15   The inclusion criteria were identical in all

16 four studies: male or female COPD patients, greater

17 than or equal to 40 years of age, with a smoking

18 history of at least 10 pack years were eligible.

19 Patients needed to have moderate to very severe airflow

20 limitation with a post-bronchodilator FEV1 less than 80

21 percent predicted, and an FEV VC ratio of less than 70

22 percent. There was no lower limit defined for lung

1 function impairment. Patients with a history of asthma

2 were specifically excluded.

3   Now, a unique feature of the pivotal studies

4 was that most maintenance pulmonary medications were

5 allowed as concomitant therapy, including both short

6 and long- acting muscarinic antagonists. To our

7 knowledge, this is the first bronchodilator program to

8 allow tiotropium as concomitant therapy and required

9 special considerations.

10   For example, randomization was stratified by

11 tiotropium use to ensure a balance in tiotropium users

12 across treatment arms. While LABAs were necessarily

13 withdrawn prior to randomization, patients on LABAs

14 were allowed to switch to ipratropium. Albuterol was

15 provided to all patients as rescue medication

16 throughout the studies. And in addition to

17 bronchodilators, low-dose oral steroids, inhaled

18 steroids and xanthines were also allowed as concomitant

19 therapy.

20   Two hundred to 230 patients were randomized

21 per treatment arm in each of the four studies. In all

22 studies, demographics were reasonably well-balanced

1 across treatment arms. The majority of patients were

2 male, with a mean age just under 65 years. About two-

3 thirds of the patients were white, and about one-third

4 Asian. Current smokers and ex-smokers were well

5 represented, with a mean smoking history of 40 to 50

6 pack years.

7   There was a high use of maintenance

8 bronchodilator and anti-inflammatory therapy in the

9 studies. At study entry, about half the patients were

10 treated with either short or long-acting muscarinic

11 antagonists, and about half were treated with inhaled

12 steroids or xanthines. Patients continued to receive

13 these medications as maintenance therapy throughout the

14 trial.

15   Combination therapy was prevalent, with more

16 than 25 percent of patients treated with both

17 muscarinic antagonists and anti-inflammatories, and

18 this was true for patients across all GOLD stages. Of

19 the 37 percent of patients treated with LABAs prior to

20 study entry, just over half were also on muscarinic

21 antagonists.

22   At screening, mean pre-bronchodilator FEV1

1 ranged from 1.16 to 1.25 liters, while mean post-

2 bronchodilator FEV1 was approximately 50 percent

3 predicted normal. The mean pre to post change ranged

4 from 150 to 172 mils, or 14 to 17 percent. While the

5 majority of patients were either GOLD II or III, GOLD

6 IV patients were also represented.

7   Just over 80 percent of patients completed

8 the full 48 weeks of treatment in each study. The main

9 reasons for premature discontinuation were adverse

10 events, lack of efficacy, and consent withdrawn. Over

11 90 percent of patients completed at least up to the

12 primary endpoint in Studies 11 and 12, and just under

13 90 percent in 13 and 14. In all four studies there was

14 a higher rate of discontinuation in the placebo arm

15 compared with the active treatments.

16   Now I'll provide some more detail on our lung

17 function endpoints and the results from our pivotal

18 trials. FEV1 AUC 0-3 and trough response were per-

19 specified as primary endpoints in all four studies.

20 AUC 0-3 was based on post-dose measurements and

21 represented the peak bronchodilation. Trough was based

22 on pre-dose measurements and represented

1 bronchodilation at the end of the dosing interval.

2   In 11 and 12, the primary analysis was

3 prespecified to be conducted after 12 weeks, which

4 complied with U.S. regulatory requirements. In 13 and

5 14, the primary analysis was conducted after 24 weeks,

6 which complied with European requirements.

7   A hierarchical testing strategy was

8 prespecified to protect against Type 1 error. Ten

9 micrograms was tested first, based on AUC 0-3 and then

10 trough. Five micrograms was tested next, again based

11 on AUC 0-3 and then trough.

12   In studies 13 and 14, if all lung function

13 tests were successful, testing continued for the TDI

14 and the SGRQ based on the combined dataset. First,

15 testing for the TDI focal score was performed, first

16 for 10 micrograms and then for 5 micrograms. And if

17 the TDI focal score test was successful, testing for

18 the SGRQ total score was performed, first for 10

19 micrograms and then for 5 micrograms.

20   A full analysis set, or FAS, was prespecified

21 for the primary efficacy analysis consistent with the

22 intent to treat principle. The FAS included all

1 patients with baseline data, at least one dose of study

2 drug, and at least one on-treatment measurement. In

3 our presentation, in all four pivotal trials, the

4 primary analysis uses a mixed-effects model for

5 repeated measures, or MMRM, with categorical covariates

6 at treatment, tiotropium use stratum, test day, and

7 treatment by test day interaction, and continuous

8 covariates of baseline and baseline by test day

9 interaction.

10   As explained in our briefing document,

11 specific interaction terms in our prespecified model

12 were removed to appropriately weight the tiotropium

13 strata in proportion to stratum size. This was done

14 after unblinding in trials 11 and 12, and prospectively

15 applied for analysis of trials 13 and 14 prior to

16 unblinding.

17   Now there are some novel features of our

18 clinical program, most notably with regards to the

19 inclusion of patients in GOLD IV, and the allowance of

20 usual care background therapy. So we assessed the

21 clinical relevance of the lung function improvements

22 for olodaterol in a number of ways within the Phase III

1 program.

2   These include assessment of SABA

3 responsiveness in all patients to compare with the

4 bronchodilator response for olodaterol, direct

5 comparison with active comparators of known therapeutic

6 benefit, evaluation of symptomatic benefit, and in two

7 studies, evaluation of lung function efficacy under

8 traditional trial conditions.

9   So this figure shows the adjusted mean FEV1

10 profile pre-dose, and up to three hours after the first

11 dose, for Study 11. Olodaterol 5 micrograms is orange

12 and placebo is gray. There's clear evidence of

13 bronchodilation with olodaterol five minutes after

14 dosing. The bottom figure shows the profiles after 12

15 weeks. Bronchodilation is evident at one hour and at

16 10 minutes prior to dosing, with a further increase

17 after dosing. And here we see similar results from

18 Study 12.

19   Now we will look at the AUC 0-3 and trough

20 response over the 48-week treatment period. In Study

21 11, AUC 0-3 response was significantly greater for

22 olodaterol, compared to placebo, at all visits. Trough

1 response was also significantly greater for olodaterol

2 compared to placebo at all visits. And again, we see

3 comparable results in Study 12. For reference, the

4 arrows indicate the primary endpoints after 12 weeks.

5   Moving to Studies 13 and 14, we'll now review

6 the FEV1 profiles after the first dose and after 24

7 weeks. In Study 13, there is clear evidence of

8 bronchodilation with olodaterol five minutes after the

9 first dose, with an onset of effect comparable to

10 formoterol shown here in green. After 24 weeks,

11 bronchodilation is evident for both olodaterol and

12 formoterol prior to dosing, with a further increase

13 after dosing. And we see consistent results in the

14 replicate Study 14.

15   Now we'll look at the AUC 0-3 and trough

16 response over the 48-week treatment period. In Study

17 13 AUC 0-3 response was significantly greater for

18 olodaterol and formoterol, compared to placebo, at all

19 visits. Trough response was also significantly greater

20 for olodaterol and formoterol compared to placebo at

21 all visits, except for an isolated visit after 40

22 weeks. There were no significant differences between

1 olodaterol and formoterol at any visit for either AUC

2 or trough. And once again, we see comparable results in

3 Study 14. As noted earlier, the arrows indicate the

4 primary endpoints, this time after 24 weeks.

5   According to the analyses used by BI, with

6 tiotropium strata weighted by stratum size, olodaterol

7 5 micrograms met its primary endpoints in Studies 11

8 and 12, with statistically significant increases in AUC

9 0 to 3 and trough response compared to placebo after 12

10 weeks. And in Studies 13 and 14 with statistically

11 significant increases in AUC 0-3 and trough response

12 compared to placebo after 24 weeks.

13   Now as you've seen in the FDA briefing

14 document, when using the prespecified analysis in Study

15 12, with equal weighting for the tiotropium strata, the

16 difference between olodaterol and placebo after 12

17 weeks was not significant. But when considering the

18 totality of the data, we have concluded that there is

19 clear evidence of a bronchodilator effect for

20 olodaterol 5 micrograms once- daily.

21   Now we performed a variety of exploratory

22 analyses to evaluate the efficacy of olodaterol across

1 subgroups. We explored the influence of baseline

2 spirometry in a number of ways, illustrated here for

3 AUC 0-3 response for the 11 and 12 combined dataset.

4 We divided patients into subgroups based on pre-

5 bronchodilator FEV1, as well as post-bronchodilator

6 FEV1 based on GOLD stages. As expected, patients with

7 a higher baseline FEV1 had a greater effect size for

8 FEV1 response.

9   We also explored the influence of SABA

10 responsiveness by using the ATS-ERS criteria of greater

11 than 12 percent in 200 mils, as well as by using the 12

12 percent increase only. Again, as expected, patients

13 with an increased SABA responsiveness had a greater

14 effect size for FEV1 response.

15   We also performed subgroup analyses based on

16 a variety of demographic factors. There was some

17 evidence of a lower response in Asians compared to

18 whites, though it should be noted that Asian patients

19 had a lower baseline FEV1 and a reduced responsiveness.

20 There was a lower response in patients using xanthines,

21 but the smaller number of patients in this subgroup

22 meant that the confidence intervals were rather wide.

1 There was also a lower response in patients using

2 SAMAs.

3   Finally, while there was a lower response in

4 tiotropium users in individual studies, this was not

5 consistently shown in all studies, and there was no

6 clear influence of other demographic factors.

7   Now for feasibility reasons, the pivotal

8 studies only measured lung function up to three hours

9 post-dose. Therefore Studies 24 and 25, and Studies 39

10 and 40, were designed to assess the bronchodilating

11 profile of olodaterol over a continuous 24-hour dosing

12 interval.

13   All studies used specialized sites with

14 experience in 24-hour lung function testing. After six

15 weeks of treatment, patients performed spirometry 30

16 minutes pre-dose, up to 12 or 14 hours post-dose on Day

17 1, and then at 22, 23 and 24 hours post-dose on Day 2.

18 To ensure the quality of the Day 2 measurements,

19 patients stayed overnight in the clinic or in a hotel

20 near the clinic.

21   The bronchodilating profile was very

22 consistent across all four studies. Here we see

1 studies 39 and 40 on the left, and Studies 24 and 25 on

2 the right. All four studies showed significant

3 increases in FEV1 for olodaterol compared to placebo

4 across the full 24-hour dosing interval.

5   We will now show the profiles for the active

6 comparators for comparison. Here we see again the

7 profiles for olodaterol in Studies 39 and 40. When we

8 now add the results for once-daily tiotropium

9 HandiHaler in purple, we see that the 24-hour profile

10 of olodaterol was very similar to the profile of

11 tiotropium.

12   Here we see again the profiles for olodaterol

13 in Studies 24 and 25. We now add the results for

14 twice- daily formoterol in green. Formoterol had a

15 slightly higher peak in the morning, but also showed a

16 greater rate of decline through to 12 hours post-dose,

17 as would be expected with a twice-daily product. The

18 evening dose of formoterol resulted in a second peak,

19 however by the end of the 24 hours, the bronchodilating

20 effect was comparable between olodaterol and

21 formoterol.

22   Now let's take a moment to talk about the

1 comparison of the two doses studied in Phase III. The

2 lung function efficacy of 5 micrograms once-daily and

3 10 micrograms once-daily was comparable across the

4 majority of the Phase III lung function studies.

5   We can illustrate this by looking at the AUC

6 0-3 and trough responses over the 48 weeks in the

7 pivotal studies. Here we see the AUC 0-3 and trough

8 results for the combined dataset from Studies 11 and

9 12, 5 micrograms is in orange and 10 micrograms in

10 blue. There is minimal to no increase of effect with

11 10 micrograms over 5 micrograms. And the results are

12 similar for the combined dataset from Studies 13 and

13 14.

14   Now there is one final aspect of the lung

15 function results that deserves mention, and that is the

16 differences in effect size for lung function

17 improvements across the Phase III studies. First,

18 let's focus on the pivotal studies. Shown here are the

19 SABA responsiveness and the difference compared to

20 placebo for AUC and trough response for the total study

21 population in the pooled dataset from the four studies.

22   And now we will compare with a subgroup of

1 GOLD II and III patients not on short or long-acting

2 muscarinic antagonist, xanthines, or beta blockers

3 during the studies. In line with expectations, we see

4 higher effect sizes in this subgroup for SABA

5 responsiveness for AUC 0-3 response and for trough

6 response.

7   Now in comparing the effect size across

8 studies, we may consider several factors related to

9 differences in trial design. As highlighted in this

10 table, there were relevant differences in baseline

11 FEV1, SABA responsiveness, concomitant therapies, and

12 timing of trough FEV1 relative to dosing. Of

13 particular note, Studies 39 and 40 did not allow

14 concomitant therapy with LABAs, SAMAs or LAMAs, and as

15 such, more closely resembled trial conditions of

16 traditional bronchodilator studies in COPD.

17   Now these differences in trial design provide

18 a reasonable explanation for the differences in effect

19 size observed across the studies. Here we see the AUC

20 0-3 and trough responses in the pivotal studies and the

21 24-hour PFT studies. The effect size for olodaterol in

22 Studies 39 and 40 are notably higher compared to the

1 pivotal studies. These effect sizes, which were

2 comparable to tiotropium, are quite similar to effect

3 sizes seen for other bronchodilators in studies that

4 did not allow maintenance bronchodilator therapy.

5   So to summarize the results shown so far.

6 Consistent results were seen in all four pivotal

7 studies with a rapid onset of action after the first

8 dose, comparable to formoterol, and significant

9 increases versus placebo for the primary endpoints of

10 AUC 0-3 and trough response, comparable to 10

11 micrograms once-daily, and comparable to formoterol

12 twice-daily. Significant lung function improvements

13 were maintained up to 48 weeks.

14   And in the six-week studies, the 24-hour

15 profile for olodaterol, 5 micrograms once-daily, was

16 comparable to 10 micrograms once-daily, and comparable

17 to tiotropium HandiHaler once-daily.

18   So now let's review the symptom-based

19 endpoints assessed in Phase III. As mentioned earlier,

20 the TDI and the SGRQ were included in Studies 13 and

21 14, with the analyses prespecified to be based on the

22 combined dataset from the two studies. In all four

1 pivotal studies, daytime and nighttime use of rescue

2 medication was recorded on a daily basis by the patient

3 using an electronic diary.

4   Here we see the results for the TDI focal

5 score over 48 weeks. The focal score of greater than

6 1.5 units in all active treatment groups is indicative

7 of an improvement compared to the patient's baseline

8 dyspnea assessment. However, there was an unexpected

9 increase over time in the placebo group, so

10 consequently, while the differences between olodaterol

11 and placebo was nominally significant after 6 and 12

12 weeks, it was no longer significant after 18 weeks and

13 beyond.

14   Turning now to the SGRQ. Treatment with

15 olodaterol 5 and 10 micrograms resulted in significant

16 improvements in SGRQ total score compared with placebo

17 after 12 and 24 weeks. The difference was also

18 significant for 10 micrograms after 48 weeks, but not

19 for 5 micrograms. The difference for formoterol versus

20 placebo was significant after 12 weeks but not after 24

21 and 48 weeks.

22   Now we will take a look at the use of rescue

1 medication. Here we see the reduction in daytime

2 rescue use for olodaterol 5 and 10 micrograms compared

3 to placebo in Studies 11 and 12. Similar results were

4 observed in Studies 13 and 14. Of note, the reduction

5 in rescue use for once-daily olodaterol was comparable

6 to twice-daily formoterol.

7   Reduction in use of rescue medication was

8 also evident during the nighttime, shown here on the

9 left for Studies 11 and 12, and on the right for 13 and

10 14. And again, the reduction in nighttime rescue use

11 for once- daily treatment with olodaterol was similar

12 to that observed for twice-daily treatment with

13 formoterol.

14   So I'd like to conclude this part of my

15 presentation with an overall summary of the efficacy

16 assessment of olodaterol 5 micrograms once-daily.

17 According to the analyses based on weighting of

18 tiotropium strata proportional to stratum size,

19 olodaterol 5 micrograms met its lung function primary

20 endpoints in each of the four pivotal studies, with

21 significant improvements in AUC 0-3 and trough response

22 compared to placebo.

1   Improvements in lung function for olodaterol

2 were comparable to the once-daily LAMA, tiotropium

3 HandiHaler, and the twice-daily LABA, formoterol,

4 registered bronchodilators of known therapeutic

5 benefit. In all Phase III studies, the lung function

6 efficacy of olodaterol 5 micrograms was comparable to

7 10 micrograms.

8   And when considering the study populations

9 and co-medications used, the effect sizes observed for

10 olodaterol across the different studies were in line

11 with expectations for a once-daily bronchodilator in

12 COPD. Lung function improvements translated into

13 improvements in several symptom-based endpoints.

14   So in conclusion, the Phase III program

15 provides substantial evidence that once-daily treatment

16 with olodaterol 5 micrograms once-daily results in

17 clinically meaningful bronchodilation in patients with

18 moderate to very severe COPD.

19   So now I'd like to use the last few minutes

20 of my presentation to focus on our exercise studies.

21 Replicate Studies 37 and 38 assessed the effects of

22 olodaterol on exercise endurance time during constant

1 work rate cycle ergometry, a methodology which has now

2 become a standard for evaluating the effects of

3 bronchodilators on exercise tolerance.

4   The studies followed a six-week, randomized,

5 double-blind, placebo-controlled crossover design. The

6 primary endpoint was prespecified as endurance time.

7 And the primary analysis was conducted on log

8 transformed data to account for the non-normal

9 distribution for endurance time seen in earlier BI

10 exercise studies.

11   In addition, inspiratory capacity and

12 intensity of breathing discomfort at a standardized

13 time of exercise called isotime, were prespecified as

14 key secondary endpoints.

15   The inclusion criteria were identical to

16 those used in the other Phase III studies except for

17 the upper age limit of 75 years due to the physical

18 demands of the maximal exercise testing. Evidence of

19 lung hyperinflation was not required, which contrasts

20 with previous bronchodilator exercise studies.

21   Now a few words about the methods used for

22 the cycle test in the studies. At screening, patients

1 performed an incremental cycle to determine work

2 capacity. In this test, patients cycled for as long as

3 possible at a steady pedal rate as the work rate was

4 increased by 10 watts every minute. Work capacity was

5 defined as the highest work rate maintained for at

6 least 30 seconds.

7   All subsequent cycles were conducted at a

8 constant work rate calculated as 75 percent of work

9 capacity. Patients again cycled for as long as

10 possible at a steady pedal rate. IC maneuvers and Borg

11 ratings were carried out pre-exercise, at two-minute

12 intervals during exercise, and at the end of exercise.

13   So in this illustration, the patient has

14 completed the full minute at 60 watts, and so work

15 capacity is defined as 60 watts. The patient then

16 performs all subsequent constant work rate cycles at 45

17 watts, which is 75 percent of 60 watts.

18   The incremental cycle test and a practiced

19 constant work rate cycle were conducted at the initial

20 screening visit. A baseline constant work rate cycle

21 was conducted at visit two, prior to randomization.

22 And then further constant work rate cycles were

1 conducted at the end of the treatment period.

2   These cycles were performed two hours after

3 dosing to align with the peak bronchodilating effect of

4 olodaterol, which allowed us to optimally evaluate the

5 relationship between improvements in airflow and

6 improvements in exercise endurance time.

7   Now an important consideration when assessing

8 exercise parameters across different exercise tests is

9 to standardize the time at which parameters are

10 compared. Now since endurance time is variable across

11 tests, comparing parameters at the end of exercise is

12 problematic, but this can be overcome by using the

13 concept of isotime.

14   In this illustrative example, the shortest

15 endurance time is at baseline, and this time is defined

16 as isotime for this patient. We can see that exercise

17 data is available at this time for all tests, which

18 means for all periods in a crossover study.

19   So first, let's focus on the primary

20 endpoint. In Study 37, there was a statistically

21 significant 14 percent increase in endurance time for

22 olodaterol 5 and 10 micrograms compared to placebo.

1 This was replicated in Study 38 with a statistically

2 significant 10 to 12 percent increase.

3   In both studies, there was also a

4 statistically significant increase in IC at isotime for

5 both 5 and 10 micrograms. This reflects a reduced

6 hyperinflation during exercise and is believed to be

7 the mechanistic explanation for the observed increase

8 in endurance time.

9   In Study 37, but not 38, there was a

10 statistically significant reduction in the intensity of

11 breathing discomfort at isotime. This is consistent

12 with the prevailing view that reductions in breathing

13 discomfort during exercise provide the link between the

14 reduced hyperinflation and the improved symptom limited

15 endurance time.

16   So to conclude, Studies 37 and 38 have shown

17 that improvements in airflow limitation with olodaterol

18 translated into reduced lung hyperinflation during

19 exercise. This reduced hyperinflation then resulted in

20 significant improvements in symptom limited exercise

21 endurance time.

22   And we consider this relationship between

1 improvements in lung function and exercise endurance

2 time to be a meaningful way to further characterize the

3 bronchodilator efficacy of olodaterol. And based on

4 these results, we have proposed adding information in

5 the clinical study section of our prescribing

6 information to describe the significant increase in

7 endurance time and IC observed in each study.

8   So I'll now hand the podium over to Dr. Bernd

9 Disse who will present the safety assessment for

10 olodaterol. Safety and Risk Management of Olodaterol

11 for COPD

12   DR. DISSE: Thank you, Dr. Hamilton. Good

13 morning. I'm Bernd Disse, a physician pharmacologist

14 involved in the development of respiratory drugs for

15 many years, and my task today is to review the safety

16 of olodaterol. I will address the safety population,

17 its characteristics, and the adverse events.

18   The following three areas will receive

19 special attention, cardiovascular and respiratory

20 events is of special importance for the class, and

21 neoplasms because of an imbalance observed. My review

22 includes clinical laboratory, adverse events related to

1 the drug class or to the route of administration, as

2 well as adverse events by subgroup. I will also

3 outline our risk management strategy.

4   Our safety evaluation was based on standard

5 adverse event reporting and evaluation by preferred

6 terms, as well as predefined aggregated terms, which

7 were standard medical dictionary based queries, and

8 Boehringer Ingelheim defined pharmacovigilance terms.

9   We performed vital status follow-up for all

10 patients throughout the planned observation period in

11 the 48-week studies, and achieved over 98 percent

12 completeness. Following advice of the FDA, all

13 respiratory serious adverse events and deaths were

14 submitted to blinded adjudication by an independent

15 committee.

16   Cardiovascular safety received special

17 attention. All patients received ECG and 772 wore

18 Holter monitors at several time points. Inhaled

19 administration- related paradoxical reactions were

20 captured as symptoms of bronchoconstriction.

21   The primary safety population includes more

22 than 3,000 COPD patients in two pairs of replicate 48-

1 week studies. More than 83 percent, so more than 1,470

2 patients, were treated for 330 days or longer with

3 olodaterol 5 or 10 microgram. Of note, day 330 was the

4 earliest completion visit.

5   We derived supportive information from 1,800

6 COPD patients and 270 healthy volunteers in shorter

7 duration Phase I to III studies, and from more than 700

8 patients with asthma.

9   The demographics in the 48-week studies were

10 balanced across the treatment groups, with small

11 differences unlikely of clinical relevance. The

12 typical COPD patient was 64, male, most were white,

13 with a significant contribution of Asian patients. The

14 number of African-American participants was limited,

15 overall 89, and of these 39 in the 48-week studies. We

16 recorded a mean smoking history of 46 pack years, and

17 more than one- third of our patients were still smoking

18 at entry into the study.

19   The long-term safety population includes

20 patients with moderate to very severe COPD. Using the

21 GOLD guideline, lung function based severity

22 classification, about 50 percent were moderate, 40

1 percent severe, and 10 percent very severe Stage IV.

2 Comparing COPD severity in the treatment groups, a

3 higher proportion of Stage IV in placebo appears

4 balanced out by a lower proportion of Stage III, so

5 overall severity was grossly balanced across the

6 groups.

7   As Dr. Hamilton has outlined, patients

8 generally continued baseline medication during the

9 course of the studies, except long-acting beta

10 agonists. Many patients used concomitant treatments

11 and beyond pulmonary medication. For example, 65

12 percent used any cardiovascular medication. Of note,

13 beta blockers were not strictly excluded as many COPD

14 trials, and 10 percent used these drugs.

15   Now to review comorbidities at baseline.

16 Cardiac disorders, based on terms for coronary artery

17 disease, as well as history of neoplasms, were included

18 at a higher frequency in the olodaterol groups than

19 placebo. We think the Phase III population represents

20 typical COPD and the results are relevant for clinical

21 use.

22   Premature discontinuation was about seven

1 percent more frequent in the placebo groups than in

2 active treatment, which is a common observation with

3 medication offering symptomatic improvement. Most

4 patients discontinued for respiratory adverse events,

5 worsening of disease under study, or lack of efficacy.

6   Next, the review of all adverse events on

7 treatment by preferred term as reported by the

8 investigator and system organ class. About 70 percent

9 of our patients reported adverse events with small

10 differences between the treatment groups. Severe and

11 serious adverse events were not different between the

12 treatments. Related adverse events were numerically

13 lower in olodaterol than placebo.

14   Fatal adverse events on treatment were

15 grossly balanced, but numerically higher in the

16 formoterol and olodaterol 10 microgram groups. This

17 will be reviewed in more detail, including the vital

18 status follow-up. Other serious adverse events, as

19 reflected in this table, were reported at low and

20 similar frequencies across the groups.

21   This bar graph reviews adverse events by

22 system organ class, including all terms reported more

1 frequently than two percent in any olodaterol group.

2 Most classes were balanced across the treatments. A

3 slightly higher frequency was seen for olodaterol in

4 infections and infestations, and for all active

5 treatments in musculoskeletal terms. Conversely, in

6 the respiratory system organ class, the active

7 treatment groups had a lower frequency than placebo.

8   With the next three slides I will review the

9 system organ classes showing differences by the

10 preferred term. In infections and infestations, the

11 higher frequency for olodaterol is mainly due to the

12 preferred term nasopharyngitis. Urinary tract

13 infection was reported more frequently in both

14 olodaterol groups. However a review of the cases

15 indicates that most were secondary events, for instance

16 following surgical intervention. Therefore a causal

17 relationship is unlikely. Nasopharyngitis was

18 identified as an adverse drug reaction and noted for

19 our proposed label.

20   As for respiratory events, the generally

21 lower frequency for olodaterol 5 is due to the

22 preferred term COPD, which means aggravation of

1 disease. In musculoskeletal and connective tissue

2 disorders the higher frequency for active treatments

3 versus placebo is mainly due to the terms back pain and

4 arthralgia. For formoterol muscle spasms were reported

5 more frequently in addition. These adverse events are

6 known side effects of the class of beta agonists.

7 Arthralgia was identified as an adverse drug reaction

8 and noted for the proposed label.

9   This table displays all serious adverse

10 events affecting more than two patients per preferred

11 term. Respiratory events were lower in the olodaterol 5

12 group versus placebo, but not in 10 microgram.

13 Infections overall showed small differences between the

14 treatment groups. Cardiac disorders and nervous system

15 disorders were higher in placebo. Neoplasms, malignant

16 unspecified, were higher in all active treatment groups

17 versus placebo and I will analyze this in more detail

18 in a moment. Injury and procedural complications were

19 numerically higher in the olodaterol groups. The

20 preferred terms fall or joint dislocation, based on

21 case review, do not point to a causal relation to beta

22 agonist treatment. Musculoskeletal terms were higher

1 in all active treatment groups versus placebo, and are

2 known class effects of beta agonists.

3   In this table a summary of all deaths from

4 all studies. Overall the death frequency was similar

5 across the treatment groups. Next, the shorter

6 duration Phase I and II studies, including the Phase

7 III crossover studies. In COPD four fatal events were

8 seen in the olodaterol 10 microgram group, however the

9 association with treatment is not strict in crossover

10 studies. For instance, two of these fatal events were

11 observed in the washout period between four week

12 treatments. In the Phase II studies in asthma, or in

13 healthy volunteers, no cases of death were observed.

14   Now the 48-week studies. On treatment death

15 was numerically higher in olodaterol 10 and formoterol.

16 However, when we include vital status information for

17 the patients who discontinued early, which means the

18 total number includes now on-treatment, post-treatment

19 and post-study events, then the fatality rate was

20 balanced across treatment groups. Seven of the fatal

21 events were reported after the planned exit date of day

22 351. Censoring by this planned exit date can ensure

1 comparable duration and completeness of observation for

2 study completers and early discontinued. Now following

3 this approach, all active treatments were numerically

4 lower than placebo.

5   In this table all deaths on treatment were

6 assigned to system organ classes based on the

7 adjudicated causes of death. The following imbalances

8 were observed:

9   olodaterol 5 with more COPD exacerbation

10 events; olodaterol 10 with more neoplasms; formoterol

11 with more cardiovascular events; and placebo with more

12 cardiovascular events, too.

13   Considering that olodaterol and formoterol

14 are members of the same drug class, there is no

15 biological explanation or plausibility for a changing

16 pattern of system organ class predominance in the

17 treatment groups. Imprecision in assigning a primary

18 cause and variability at low numbers are more likely

19 explanations for these numerical differences. As

20 outlined in the previous table, the overall fatality

21 rate, including vital status of early discontinued

22 patients, was balanced across the treatments.

 1   Now the review of areas of special interest:

 2   cardiovascular, respiratory and neoplasms.

 3 In this table major adverse cardiovascular events. The

 4 composite MACE was defined as fatal cardiac or vascular

 5 events or sudden death. Non-fatal MACE includes non-

 6 fatal myocardial infarctions and stroke in addition.

 7 All MACE and fatal MACE events were lower in both

 8 olodaterol groups compared to placebo, with most rate

 9 ratios lower than 0.5 but confidence intervals still

10 included 1.

11   With this table, I'll review cardiac events

12 in more detail by exposure, adjusted risk ratios and

13 confidence intervals. For the system organ class the

14 risk for olodaterol is numerically lower than placebo.

15 The confidence intervals include 1 for the system organ

16 class overall, as well as for all individual terms.

17   Among the individual terms, ventricular

18 tachyarrhythmias and cardiac failure were numerically

19 higher for olodaterol 5, but only slightly higher for

20 10, so no dose ordering. Myocardial infarction was

21 lower with 5 but higher with the 10 microgram dose,

22 whereas other ischemic terms were lower with both doses

1 of the active. Given that imbalances are small and

2 show no dose ordering, a causal relation to treatment

3 is considered unlikely.

4   Now turning to respiratory events. In all

5 studies longer than seven days, reports of death,

6 hospitalization or intubation related to asthma, COPD

7 or pneumonia, were adjudicated by an independent

8 blinded committee. The overall frequency was balanced

9 across placebo and olodaterol groups, slightly higher

10 for formoterol.

11   Total or key respiratory events were balanced

12 across olodaterol groups and placebo, slightly higher

13 with formoterol. Pneumonia and other respiratory

14 related events were higher for olodaterol 10 and

15 placebo, only slightly higher for the 5 dose and

16 formoterol. But the identification of pneumonia, based

17 on adverse event reports, is not precise and not

18 necessarily based on x- ray, so partially overlaps with

19 COPD.

20   Also, the adjudicated terms were not

21 corrected for exposure, which was longer in active

22 treatments. COPD exacerbations were defined as an

1 efficacy endpoint and showed no difference, as

2 indicated by hazard ratio for time to first of 0.9 for

3 olodaterol, or 1 for the 10 microgram dose.

4   Now exacerbations based on standard adverse

5 event reporting with a look at incidence rates and risk

6 ratios. The relative risk was lower for olodaterol 5

7 microgram compared to placebo, and the confidence

8 interval excludes 1. This finding was consistent for

9 the preferred term and aggravated pharmacovigilance

10 terms. For the 10 microgram dose, the rate ratio was

11 close to 1.

12   For COPD exacerbations broad, including

13 pneumonia, the risk was still lower than placebo for

14 both olodaterol dose groups. As a conservative

15 conclusion, the risk of COPD exacerbations with

16 olodaterol treatment is comparable to placebo, which

17 already allowed standard of care.

18   Now I'd like to take up neoplasms.

19 Neoplasms, malignant and unspecified and reported as

20 serious adverse events were more frequent in all active

21 treatment groups versus placebo. To analyze in depth,

22 we included all serious or non-serious events reported

1 in the system organ class, but then excluded non-

2 malignant cases. Doubtful or unspecified cases were

3 kept. Following this, malignant and potentially

4 malignant neoplasms were higher in the olodaterol 10

5 microgram group.

6   In the following two tables, I will review

7 the individual events by preferred term to identify any

8 potential pattern or cluster. Here the first part of

9 malignant or unspecified neoplasms by preferred term.

10 The distribution of tumor types and locations is

11 diverse, and there's no pattern that would suggest a

12 relation to treatment. Apart from several skin

13 cancers, only individual cancer types and locations

14 were reported.

15   In this second part, the reported tumors

16 overall reasonably reflect type and locations as may be

17 expected in a population of this age and smoking

18 history. The only tumor site with increased frequency

19 is the lung, for the 10 microgram olodaterol group,

20 with six events of verified lung cancers, and in the

21 third line here, a few more cases of lung nodules, not

22 malignant or unclear, and lung metastases indicated in

1 the brackets. In the middle part of the table, the

2 primary tumors to the mentioned lung metastases and one

3 event of liver metastases originating from a primary

4 small cell lung cancer.

5   The tumors in this field and in the lower

6 part of the table fall into diverse categories. From

7 this review, we conclude that apart from the six cases

8 of verified lung cancer in the olodaterol 10 group,

9 there are no unusual findings in this dataset.

10   So now we focus on the verified cases of lung

11 cancer. This slide summarizes the time to diagnosis.

12 The shaded horizontal area defines a minimal latency

13 period. Tumors diagnosed before four to six months are

14 highly unlikely to be influenced by drug exposure.

15   One case in the olodaterol 5 group was in

16 fact pre-existing at screening. One patient with small

17 cell lung cancer was diagnosed after six days into the

18 study. And two patients presented with widespread

19 metastatic disease within four months. So the majority

20 of cases is consistent with preexisting disease.

21   Finally, when we look at incidence rates and

22 relative risks of these neoplasms, malignant or non-

1 specified, there are slight imbalances for olodaterol

2 10 and formoterol with wide confidence intervals

3 including 1. To be noted, non-clinical investigations

4 do not indicate any mutagenic or carcinogenic potential

5 of olodaterol, other than known class effects of beta

6 agonists in rodents in high doses. And there's no

7 clinical evidence that beta agonists may promote cancer

8 growth. So we conclude that a carcinogenic effect of

9 olodaterol, or of beta agonists in general is unlikely.

10   I will now to turn clinical laboratory class

11 and administration related adverse events. Small

12 increases in creatinine phosphokinase were observed for

13 all active treatments compared to placebo, but not

14 versus baseline, which was statistically significant at

15 individual time points.

16   Shifts out of normal range were more frequent

17 in the active treatment groups, and most frequent in

18 the formoterol group. However, affected patients did

19 not have increased adverse events. This is considered

20 a typical laboratory finding for the class of beta

21 agonists and we do not consider it clinically relevant.

22   We observed trends in decreases of potassium

1 in healthy volunteers only at higher doses, starting

2 with 10 to 20 micrograms. In the 48-week studies,

3 there was no relationship between olodaterol plasma

4 levels and potassium concentrations, or shifts to below

5 lower limit of normal. Olodaterol treatment had no

6 impact on plasma glucose.

7   In this table, potential drug class related

8 events if more frequent than two percent. Most of the

9 typical class effects like tachycardia, arrhythmia,

10 palpitations, myocardial ischemia, angina,

11 hypertension, tremor, headache, nervousness, insomnia,

12 dizziness, hypokalemia and hypoglycemia were not

13 observed more frequently for olodaterol 5 compared to

14 placebo. Arthralgia, myalgia, muscle weakness were

15 reported more frequently with the active treatment

16 groups. In addition, dizziness and hypertension were

17 identified in comparison to formoterol as these are

18 labeled adverse drug reactions for formoterol.

19   Local tolerability is an important area to

20 investigate for inhaled drugs. Therefore we recorded

21 respiratory symptoms, or drop in airflow, in relation

22 to time of administration. Drop in airflow was at a

1 lower frequency in olodaterol compared to placebo,

2 indicating the efficacy of the beta agonist. The

3 affected proportion of placebo patients, of about 10

4 percent, is in the range we typically see in inhaler

5 trials. Symptoms of administration related cough,

6 wheeze, or dyspnea were not observed at all, also not

7 with placebo, indicating that the Respimat spray is

8 well tolerated.

9   As final portion of my presentation, subgroup

10 analysis for adverse events, safety in other studies,

11 especially asthma and risk management. We conducted

12 subgroup analyses of all adverse events displayed here

13 by rate ratios, olodaterol 5 microgram over placebo,

14 confidence intervals and forest plots.

15   The relative risk was balanced across

16 intrinsic factors including gender, age, race, region

17 and smoking status. This holds true for subgroups of

18 different COPD severity, or renal impairment, or groups

19 with or without cardiac disease at baseline. The

20 relative risk in subgroups is consistent with the

21 overall population.

22   The rate ratio was also balanced across

94

1 extrinsic factors and concomitant conditions. As

2 displayed by the forest plots, the relative risk was

3 not different in subgroups based on co-medication,

4 common respiratory drugs and beta blockers, consistent

5 with the overall relative risk, also concomitant

6 conditions, reversibility to beta agonist, creatinine

7 phosphokinase shift or diabetes.

8   We do not plan to seek an indication in

9 asthma, but studies in asthma are of value to inform

10 the safety discussion in the COPD program. Life-

11 threatening or disabilitating (sic) events were not

12 observed. Adverse events, serious adverse events or

13 events leading to discontinuation were balanced across

14 treatment groups in asthma. As noted in our briefing

15 document, adverse events in the Phase II asthma and

16 shorter duration COPD studies were consistent with the

17 48-week studies in COPD.

18   Our development program included a broad

19 range of moderate to very severe COPD patients with

20 many comorbidities and state of the art co-medication.

21 The safety profile includes 1,500 patient years in

22 controlled parallel group studies and provides a

1 favorable safety record even at double the proposed

2 dose.

3   The rate of treatment discontinuation was

4 lower in olodaterol than placebo. The overall

5 frequency of adverse events was comparable in the

6 olodaterol, formoterol and placebo groups. While

7 pneumonia appeared more frequent in the olodaterol 10

8 microgram group, but not in 5, the frequency of the

9 inclusive term key respiratory events was similar

10 across all groups.

11   Malignant neoplasms, while numerically more

12 frequent in the olodaterol 10 microgram and formoterol

13 groups, the tumor types and locations were diverse and

14 typical for a patient population of this age and

15 smoking habit.

16   A review of the lung cancer cases suggested

17 pre- existing disease considering the latency period.

18 Non- clinical carcinogenicity and mutagenicity

19 investigations indicated that there is no evidence of

20 biological plausibility for a carcinogenic potential of

21 olodaterol in man.

22   Arthralgia, hypertension, dizziness and

1 nasopharyngitis were identified as adverse drug

2 reactions and are typical for the class. No overall

3 safety concerns were identified among any patient or

4 co- medication subgroup. Based on these data, we

5 conclude that olodaterol offers a positive benefit to

6 risk in patients with COPD.

7   I would like to complete my presentation with

8 an outline of our risk management plan. Olodaterol is

9 not marketed in any country. We are committed to

10 working with the agency to create appropriate product

11 information that clearly excludes treatment of asthma.

12   Our pharmacovigilance program includes

13 predefined signal detection algorithms. Ongoing large

14 studies in combination development will substantially

15 enlarge the safety database in COPD. Our proposed risk

16 evaluation management strategy is based on a

17 communication plan and periodic assessment.

18   And now I would like to ask Dr. Casaburi to

19 return to the podium and conclude with his perspective

20 on how olodaterol would fit into the current COPD

21 armamentarium. Thank you for the attention. Clinical

22 Summary and Perspective on the Use of Olodaterol for

 1 Patients with COPD.

 2   DR. CASABURI: Good morning again. I've been

 3 asked to give my clinical perspective as a

 4 pulmonologist on the use of olodaterol in COPD

 5 patients. We can consider COPD treatment approaches

 6 from the perspective of what the GOLD guidelines say

 7 the goals of COPD treatment are.

 8   According to the GOLD guidelines, we'd like

 9 to relieve symptoms. We'd like to improve exercise

10 tolerances. This is a major goal. We want to improve

11 health status, their quality of life. We'd like to

12 prevent and treat disease exacerbations. We'd like to

13 prevent disease progression. And we'd like to reduce

14 mortality.

15   Now bronchodilator therapy, and specifically

16 olodaterol, actually does have an effect on a

17 substantial number of these, relieving symptoms,

18 improving exercise tolerance, and improving health

19 status. Slowing disease progression has proven to be a

20 very difficult goal to achieve, and so has decreasing

21 mortality. On the other hand, we've made some progress

22 towards preventing exacerbations.

1   We can consider what olodaterol does to

2 address important COPD goals. First of all, it's an

3 effective bronchodilator. We've seen a rapid onset of

4 action. FEV1 increases at five minutes after the first

5 dose, by a clinically appreciable amount. We've seen

6 sustained improvement in lung function after 24 hours,

7 with peak FEV1 ranging from about 160 to about 210

8 milliliters, and trough FEV1 ranging from 70 to about

9 130 milliliters across multiple studies.

10   Importantly, improved lung function is

11 obtained against a background of concomitant

12 maintenance bronchodilator therapy, including both long

13 and short- acting muscarinics, inhaled steroids and

14 xanthines.

15   Addressing another goal in the COPD

16 guidelines we see evidence of symptomatic benefit.

17 Evidence comes primarily through reduced rescue

18 medication use, specifically reduced albuterol rescue

19 use of 20 to 30 percent. Further support is provided

20 by nominally statistically significant improvements in

21 health-related quality of life as measured by a

22 reduction in the St. George's Respiratory Questionnaire

1 Total Score, although the MCID was not reached. We

2 also saw a trend towards reduction in dyspnea scores.

3   We've seen evidence of improved exercise

4 tolerance from two six-week, randomized, double-blind,

5 placebo-controlled, crossover exercise trials conducted

6 in the exercise physiology laboratory using constant

7 work rate exercise testing. Double-blinding and the

8 crossover design reduced the effect of psychological

9 and other non- COPD-related factors on the results.

10 These studies demonstrate the linkage of improved

11 airflow to reduce lung hyperinflation and dyspnea

12 during exercise, and thereby to improvements in

13 exercise tolerance.

14   Here we see a forced expiratory maneuver from

15 which we can measure FEV1; the COPD patient then

16 respires at rest and during exercise. As I described

17 in my first talk, because the patient cannot breathe

18 out fast enough, hyperinflation occurs bringing the

19 patient to high lung volumes that are associated with

20 intolerable dyspnea. After an effective bronchodilator,

21 the forced maneuver shows faster expiration. This

22 means that hyperinflation is slower to develop,

1 therefore the patient can exercise for a longer time.

2   This linkage is what we observed in the

3 olodaterol clinical trials. This plot's for Study 37

4 and 38 results in the period in which the patient

5 received placebo and the results in the period in which

6 the patient received olodaterol 5 micrograms. So

7 olodaterol increased expiratory airflow, measured by

8 FEV1, but placebo did not.

9   The increased expiratory airflow resulted in

10 increased isotime inspiratory capacity, signifying less

11 dynamic hyperinflation. Less dynamic hyperinflation

12 yielded less dyspnea at isotime, and because the

13 patient was less dyspneic, exercise endurance

14 increased.

15   Having information on exercise tolerance

16 benefits in a product label would allow for a more

17 meaningful discussion of a therapeutic benefit directly

18 tied to treatment goals. Consider the physician in the

19 office working with a patient to identify appropriate

20 management of the patient's COPD. Communication with

21 the patient should be based on concepts important to

22 the patient, compared with a rather abstract concept of

1 airflow improvement, exercise tolerance improvement,

2 which is a consequence of improving lung airflow, is

3 easily understood.

4   Let's turn back to talk about the clinical

5 relevance of the olodaterol program in terms of its

6 effectiveness in a broad population of COPD patients,

7 that we have a well-characterized safety profile, and

8 that we have a delivery system that's easy to use.

9   In terms of effectiveness data on the drug,

10 it's been studied in a broad class of COPD patients,

11 including a full range of moderate, severe and very

12 severe COPD patients with co-morbidities typical of

13 COPD patients, and who were on concomitant medications.

14 This is an alternative therapy to what we have now, and

15 it has the potential to combine with other therapies in

16 the future.

17   The effect size and lung function meets

18 expectations for a population with a wide range of

19 severities and who are already receiving a variety of

20 other maintenance bronchodilators. The next two slides

21 help us to understand these two separate issues.

22   This slide allows comparison of

1 bronchodilator response across GOLD stages, GOLD II to

2 IV. These are what we saw in the pooled studies.

3 We've plotted the acute response to albuterol seen at

4 baseline in comparison to the response we observed over

5 the first three hours after dosing with olodaterol.

6 Note that the magnitude response of the two drugs are

7 very similar, and that the absolute increase in FEV1 is

8 less in the very severe COPD patient.

9   But importantly though, if we express the

10 olodaterol response as a percent increase, all stages

11 have roughly a 12 percent increase. This demonstrates

12 that all severities get a clinically appreciable

13 benefit.

14   This shows us the average FEV1 improvement

15 observed in six of the olodaterol studies several

16 months after starting therapy. On the left are the

17 FEV1 increases over the three hours after

18 administration, and on the right are the trough

19 responses. The orange bars are the responses to

20 olodaterol, green to formoterol, and purple to

21 tiotropium.

22   We see that there are substantial responses

1 in both measures to all drugs, but there seems to be

2 two groups here with distinctly different responses.

3 The two bars on the right in each panel show responses

4 that are clearly greater than the other three

5 responses, and we might wonder why this occurs.

6   The answer is that in these two cases,

7 patients were on tiotropium, or were on olodaterol, but

8 no other maintenance bronchodilator therapy was

9 allowed. In the other three bars, patients were

10 allowed to be on maintenance therapy and apparently

11 patient responses were limited somewhat.

12   It seems that in clinical trials where we

13 allow background maintenance therapy, our expectations

14 on the size of the bronchodilator response will have to

15 be tempered somewhat. The inclusion of very severe

16 patients and allowance of background therapy is

17 reflective of COPD patients seen in clinical practice.

18   We've seen that safety is well-characterized

19 from 48-week studies with an extensive database

20 including 28 studies with over 4,000 people with COPD.

21 Four of these were 48-week, double-blind, placebo-

22 controlled trials with over 3,000 patients.

1 Importantly, there are data for both 5 and 10 microgram

2 doses. The proposed dose is 5 micrograms, but a large

3 number of subjects were on twice the dose. Good safety

4 was demonstrated with even twice the proposed dose.

5   Finally, we have clinical relevance in terms

6 of convenience. Once daily dosing is likely to improve

7 compliance. And the Respimat device is a multi-dose

8 inhaler that generates a slow-moving mist. It may

9 reduce the need of the patient to as closely coordinate

10 their inhalation with dosing, as is necessary with a

11 metered dose propellant inhaler. There's also a dose

12 indicator that helps the patient know how much of the

13 medication is left in the inhaler.

14   I thought I'd give my clinical opinion of

15 what kind of patients might benefit from olodaterol. I

16 can see two examples. First is a somewhat younger

17 patient with COPD who is occasionally symptomatic, has

18 moderate disease, and is at low risk for exacerbations,

19 but is not adequately controlled on short-acting

20 bronchodilators. Adding a drug olodaterol would be very

21 reasonable.

22   The second kind of patient might be older,

1 have a more severe disease, and already be on

2 maintenance anticholinergic therapy. But this patient

3 continues to have symptoms, including compromised

4 exercise tolerance. Adding olodaterol would make good

5 sense in this patient.

6   So in conclusion, as we've seen this morning,

7 the sponsor conducted a total of 10 Phase III studies

8 that showed olodaterol improved lung function in

9 patients with moderate to very severe COPD. These

10 improvements were clinically meaningful in the context

11 of background therapy.

12   We've also seen in two of these studies that

13 olodaterol improves exercise tolerance. Safety is

14 well- characterized, even with twice the proposed dose.

15 Based on everything we've heard today, olodaterol

16 provides a safe and effective option for once-daily

17 bronchodilation with a multi-dose delivery system.

18   It will enhance the clinician's armamentarium

19 for COPD therapies. Thank you very much for your

20 attention this morning. I'd like now to invite Dr.

21 Disse to return to the podium to address any questions

22 you might have.

1   DR. JACOBY: Before we proceed with

2 questions, I'd like to ask Mr. Rodney Mullins to

3 introduce himself.

4   MR. MULLINS: Yes, my name is Rodney Mullins,

5 a director with National Public Health Advocates.

6 Clarifying Questions to the Presenters

7   DR. JACOBY: Thank you. Okay, questions.

8 Yes, Dr. Thadani?

9   DR. THADANI: Thadani. I have several

10 questions for you, one for your pilot studies for

11 approval, and some more specific for exercise tolerance

12 because that's pivotal to the discussion. Regarding

13 the population base, I see there were several American

14 studies and yet the representation of African-Americans

15 is only one to three percent. So you really can't --

16 does it mean there's no COPD -- I'm a cardiologist

17 asking a question - - there's no COPD in African-

18 Americans or you purposely excluded those patients are

19 difficult to do?

20   DR. DISSE: No, certainly not. African-

21 Americans have a similar rate of COPD than other

22 ethnicities. So our studies were of course not limited

1 in any way for the inclusion of other ethnicities. But

2 to be regretted, the participation of African-American

3 patients, as in many other studies, was very limited.

4   So in the U.S. part of the study, it was up

5 to four or five percent, overall then worldwide of

6 course this amounts to one to two percent. So as I

7 mentioned, it is some 30, some 40 patients in the Phase

8 III studies. This at least allows a kind of anecdotal

9 review of safety and efficacy.

10   DR. THADANI: The other question is a lot of

11 studies are 48-week studies. And yet somehow you

12 select to make the measurements at 24. Why not at 48

13 weeks? I realize there might be some attrition dropout

14 because you're studying the -- giving the drug for 48

15 weeks, there's a possibly there might be some

16 tachyphylaxis with these kind of drugs. Is that the

17 reason you pick up 24, not 48-week response? Because

18 you did measure it, and it seems like there's some

19 attrition of FEV1 especially at trough.

20   DR. DISSE: So your question relates to why

21 did we measure 48 --

22   DR. THADANI: Forty-eight weeks because your

1 studies lasted 48 weeks and yet your primary efficacy

2 is 24, rather than the later endpoint.

3   DR. DISSE: So I think that's a typical

4 procedure in clinical trial settings that the primary

5 endpoint is defined at something like 12 weeks, or in

6 the European environment 24 weeks, that's regulatory

7 precedence. It's more for the safety record that you

8 run the studies for the 48 weeks, but certainly you

9 follow through with your efficacy signal. Dr.

10 Hamilton, would you like to comment on --

11   DR. THADANI: Can -- sorry, go ahead.

12   DR. HAMILTON: Yes, certainly one of the -- I

13 guess a couple of points there in terms of why we

14 actually included both efficacy and safety in the same

15 study. So there's the alternative of, for example,

16 doing the efficacy in studies only of 12 weeks

17 duration, and some other sponsors have done that where

18 they look at 48 weeks simply for safety.

19   We felt that it was a more efficient way to

20 look at both the efficacy and the safety within the

21 same studies. As Dr. Disse had said, and as we alluded

22 to, one of the reasons for deciding on 12 weeks in the

1 11 and 12 studies and 24 was because of the standard

2 requirements for the regulatory.

3   But also we were aware, from previous

4 programs that we have conducted, that there is a

5 differential discontinuation rate, which we also saw.

6 So we were concerned about that in our design and felt

7 that would have some impact as we, certainly the

8 further you go in the studies, the more impact that was

9 going to have. So that's why we looked at the primary

10 efficacy evaluation after 12 weeks and 24 weeks.

11   DR. THADANI: Now especially to exercise

12 testing, I'm a cardiologist, I do a lot of exercise

13 studies since 1970. For angina patients, we take them

14 to angina threshold. I've done individual patient.

15 Now here, you have taken a patient, you did a step wise

16 increase in bicycle ergometer to every minute you

17 increase the watts. And then you decide to lower it to

18 75 percent, that's really done in rehab studies because

19 you know you select a lower workload so the patient can

20 walk longer.

21   Why in therapeutic studies you want to do

22 that? Because your primary endpoint is, I'm presuming,

1 your COPD patients are stopping exercise because of

2 shortness of breath, not the leg fatigue. But if it is

3 leg fatigue, that is a different issue because they

4 can't breathe.

5   And if that's the primary endpoint, why you

6 want to go to 75 percent rather than keeping that and

7 just seeing if your patient can go to a higher

8 workload? I realize you can select the workload which

9 makes them very short of breath, and keep that rather

10 than decreasing it because I really find it very

11 difficult to accept that as the primary endpoint for

12 the COPD studies.

13   It's relevant in rehab. I can see that you

14 can reduce it to 75 percent of the perceived exertion

15 and then show more improvement; that's reasonably

16 valid. But then if the dyspnea is not the primary

17 endpoint and stopping -- did you repeat a 75 percent

18 workload and make sure that before you give the double-

19 blind medication patient did stop because of dyspnea or

20 no?

21   DR. DISSE: So I trace there's two components

22 in your question. One is a justification for 75

1 percent, addressing the method. And the second, what

2 does it mean clinically. And I would like to invite

3 Dr. Hamilton to comment on the first part and Dr.

4 Casaburi to interpret the clinical relevance.

5   DR. HAMILTON: Yes, so I think I'd like to

6 maybe look at, or compare the incremental versus the

7 constant in terms of the physiology, if that's okay, as

8 a start. Because we also do measure expired air in

9 analysis in all these studies and these studies, the 75

10 percent work capacity have been conducted within a

11 number of programs over the last 10 or 15 years.

12   And what has actually been found is that if

13 you are looking at oxygen uptake, where the incremental

14 test is actually designed to measure maximum oxygen

15 uptake, when you actually look at the expired air in

16 the constant work rates, the actual VO2 is actually

17 very similar. So it is really a maximal test, so they

18 are going to exhaustion. And the VO2 levels that they

19 develop at 75 percent were capacity, are close to the

20 maximum VO2 from the incremental test.

21   DR. THADANI: So when the patient is

22 exercising, does he have mouthpiece in his, all the

1 time throughout the study or --

2   DR. HAMILTON: Yes, he does. Yes.

3   DR. THADANI: Okay. So you're measuring all

4 the data points at all the time?

5   DR. HAMILTON: Yes. We have breath-by-breath

6 analysis for all expired air. And I think you also had

7 a question about the symptom limitations. So our

8 primary look on sensory measurements is with breathing

9 discomfort, but we also, at the same time, measure leg

10 discomfort.

11   So we are measuring both breathing, intensity

12 of breathing discomfort and leg discomfort during the

13 exercise at two-minute intervals. We also do have a

14 questionnaire at the end of exercise which gives us

15 some understanding of the primary symptomatic reasons

16 for ending.

17   And in general, that's what we have found in

18 COPD patients is while there certainly is, the majority

19 of patients are limited, and I can actually show this

20 here just to show the questionnaire. So we call it a

21 locus of symptom limitation questionnaire. And so this

22 is what patients are asked after they've completed, and

1 they're asked whether they stopped because of their

2 legs or their breathing or a combination.

3   And we find it's variable, and in actual

4 fact, with some COPD patients, there are a small

5 proportion, I think it's about 15 percent, that do stop

6 because of their legs. There are a number that stop

7 because of their breathing, but a large number actually

8 stop because of both breathing and legs.

9   DR. THADANI: Thank you.

10   DR. JACOBY: Great, thank you very much. Dr.

11 Carvalho?

12   DR. CARVALHO: Thank you. I just had a

13 couple of questions also on the exercise issue. First,

14 it appeared that in Trials 37 and 38, that baseline

15 exercise endurance on patients, they would have to have

16 at least a 25 minute exercise capacity. Is that

17 correct?

18   DR. DISSE: Dr. Hamilton?

19   DR. HAMILTON: No, I think the FDA did send

20 an errata, if I'm correct. It was the other way

21 around, they had to be less than 25. So just for

22 logistical reasons, we wanted to restrict that. So if

1 a patient at the baseline had greater than 25, they

2 were excluded from the study. So all patients had to

3 have less than 25 minutes.

4   DR. CARVALHO: Thank you. And also the

5 situation with the study being done, the exercise study

6 being done two hours after dosing, is there any

7 additional data to show that that is sustained?

8   DR. DISSE: The question whether the effect

9 is sustained?

10   DR. CARVALHO: For instance, if it were to be

11 done later on in the treatment period.

12   DR. DISSE: Dr. Hamilton?

13   DR. HAMILTON: Yes. No, specifically with

14 regards to exercise, no the exercise testing was only

15 performed at two hours. One maybe additional piece of

16 information is in terms of inspiratory capacity, we did

17 measure that, both during exercise but also using body

18 plethysmography, we measured that at trough and one

19 hour post-dose. But specifically with exercise, no it

20 was only measured at two hours post-dose.

21   DR. JACOBY: Thank you. Dr. Terry?

22   DR. TERRY: I wanted to ask you the question

1 that awakened me at 3:00 this morning, and that was

2 this. You're asking us to approve olodaterol for COPD,

3 and I want to read it, "Chronic obstructive pulmonary

4 disease including chronic bronchitis and/or emphysema."

5 So you're asking us to approve it for two different

6 diseases, chronic bronchitis and emphysema, but you

7 haven't presented any of the data for each of those

8 subsets. And in fact there's a third subset, and the

9 third subset are those who have emphysema plus chronic

10 bronchitis. And so I was curious if you had that data.

11   DR. DISSE: That is correct. So we proposed

12 the traditional label, which typically is worded as

13 COPD, including chronic bronchitis and emphysema. So

14 patients with a diagnosis of COPD includes certainly

15 symptoms of chronic bronchitis.

16   There is no real attempt to diagnose a degree

17 of emphysema, and as you may realize this is also

18 pretty complicated, which in the end not -- or it's

19 unlikely to be based sufficiently on x-ray, would even

20 need a CT. But what I would like to propose is that our

21 clinical consultant, Dr. Rennard comments on this

22 question.

 1   DR. RENNARD: Thank you very much. I'm Steve

 2 Rennard from the University of Nebraska Medical Center

 3 in Omaha. I'm here today as a consultant to Boehringer

 4 Ingelheim. I've received an honorarium and my expenses

 5 have been paid.

 6   In addition, my university has received

 7 research contracts from Boehringer in the past and I've

 8 been a consultant to Boehringer in the past. I have no

 9 equity interests in Boehringer Ingelheim, and there are

10 no financial consequences or benefits to me based on

11 the outcome of today's discussions.

12   The question you raised, I can add only to

13 what Dr. Disse said, is that the labeling that's been

14 suggested I think is traditional. Chronic obstructive

15 pulmonary disease is currently defined based on the

16 spirometric criteria, which you saw presented when Dr.

17 Hamilton presented the entry criteria.

18   In general, there are two major conditions

19 that can lead to COPD, and those are emphysema and

20 chronic bronchitis. They cause airflow limitation by

21 different mechanisms, and Professor Casaburi reviewed

22 the mechanisms by which the anatomic changes can lead

1 to the airflow limitation.

2   In practice, again as Dr. Disse said, it's

3 often difficult to dissociate whether a person has

4 chronic bronchitis or emphysema, although there are

5 diagnostic methodologies. CT scanning, for example,

6 can establish the presence of emphysema. Clinical

7 features can establish the presence of chronic

8 bronchitis.

9   But in practice, this is often not done. And

10 clinically, I think we treat patients, recognizing that

11 they have chronic bronchitis and/or emphysema. But we

12 treat them based on the classification established

13 device spirometry.

14   So I think that the traditional labeling,

15 which has been suggested here, is really congruent with

16 current clinical practice, recognizing that the

17 patients haven't been categorized for their chronic

18 bronchitis or emphysema, which component would be

19 leading them to have fixed airflow limitation under

20 these circumstances.

21   DR. TERRY: Could I ask a follow-up then? In

22 your experience, are patients with pure emphysema as

1 bronchodilator responsive as patients with chronic

2 bronchitis and emphysema?

3 　　　　DR. RENNARD: Well, I guess I'll have to

4 caveat my answer that I don't know that we have good

5 ideas to who has pure emphysema and who has no

6 emphysema, and that we generally don't categorize our

7 patients in that way. I think that what we do see is a

8 spectrum of patients in COPD that have more or less

9 bronchodilator responsiveness.

10 　　　　In general, and I think we saw some data

11 presented earlier this morning, that tracks with the

12 FEV1. That is the lower the FEV1 all together, that is

13 the worse the airflow limitation, the smaller the

14 bronchodilator responsiveness in absolute terms,

15 although expressed as a percentage it becomes a little

16 bit closer.

17 　　　　I think the important point is that the vast

18 majority of patients with COPD get some degree of

19 bronchodilator response. This in fact can be variable

20 from day-to-day. There's good evidence suggesting

21 that. And some degree of bronchodilator response can

22 improve their physiology, and therefore give them an

1 opportunity to improve clinically.

2   DR. JACOBY: Dr. Tracy?

3   DR. TRACY: Obviously, we're dealing with a

4 fairly broad range of severity, and it's just kind of

5 methods question. Taking into account the background

6 medications, how high of oral steroids are we talking

7 about in this group?

8   DR. DISSE: That is about oral steroids.

9 Oral steroids were at a one to two percent figure, so

10 very low. And that at only a low dose allowed, not the

11 typical high dose used for exacerbation treatment.

12   DR. JACOBY: Mr. Mullins?

13   MR. MULLINS: Yes, my question is in regards

14 to the effectiveness of the data and to the broad

15 population, and my concerns begin with the exercise

16 trials. Could I see an overall assessment of analysis

17 of the comorbidities of the patients involved in the

18 exercise regimen? Because just the sheer way that it

19 was conducted is going to -- the ergonomics of a

20 bicycle, you will nationally exclude some patients that

21 typically are reflected into the broad population.

22   From a public health standpoint, I have

1 several concerns about exclusions and the assumptions

2 that you're making when your data is limited and

3 somewhat skewed. So my questions are I'd like to see

4 that analysis of the comorbidities of the patients

5 involved in the exercise regimen. Because to me when

6 you have patients, there are some patients that simply

7 cannot -- it's not an appropriate test for them. And

8 that's my concern.

9   And then secondly, I'd like to deal with --

10 I'll let you deal with that question first and then I'd

11 like to move to my second question.

12   DR. DISSE: Okay. Dr. Hamilton, please.

13   DR. HAMILTON: Yes, thank you. And

14 absolutely, I think that's an important consideration.

15 And in designing these studies, we've actually followed

16 the ERS taskforce standards on which patients to

17 include. So as you've rightly said, in order to make

18 sure that we were not going to have untoward events

19 during exercise, there were a number of so-called

20 contraindications to exercise, and there are quite a

21 list, and this is the list. This should be coming up

22 now, yeah. This is taken directly from the ERS

1 taskforce standardization of clinical exercise testing.

2 So we followed those standards for --

3   MR. MULLINS: Well this doesn't give me an

4 analysis of the patients involved, what percentage had

5 cardiac hypertension or -- it doesn't give me an

6 analysis of the population.

7   DR. HAMILTON: Yes, certainly. And we

8 certainly do have that.

9   MR. MULLINS: Because I want to make the same

10 assumptions that you're making. So give me that same

11 evidence so I'll feel confident that we're talking

12 about the same populations reflected in COPD

13 populations across the nation.

14   DR. HAMILTON: Yeah, we certainly do have

15 that information, unfortunately we don't have a slide

16 at the moment so we'll take a look at that in a break,

17 if that's okay, and we'll come back with that

18 information.

19   MR. MULLINS: Okay, you come back with that.

20 Okay. All right.

21   DR. JACOBY: Dr. Hoidal?

22   DR. HOIDAL: Yeah, so you, in your subgroup

1 analysis, looked at a fairly broad range related to

2 GOLD stage, age, bronchodilator response, and the

3 responses were fairly broad. Is there any subgroup of

4 COPD patients you would not recommend this drug for?

5   DR. DISSE: Not really. So we have not

6 identified a non-responsive subgroup so the response is

7 more or less, the dimension of the response is

8 variable. But say even for a GOLD IV patient, as shown

9 by Dr. Casaburi in percent of his baseline, the

10 response is appreciable.

11   DR. JACOBY: Dr. Blake?

12   DR. BLAKE: Thank you. Thank you for your

13 presentations. My question has to do with the

14 background drugs that were allowed in your long-term

15 trials, you allowed patients to be on LAMA therapies,

16 like tiotropium, but in your exercise studies you

17 didn't.

18   And so my question is, you know if patients

19 are going to be on these background drugs, how much

20 benefit can we expect, or additional benefit can we

21 expect on the exercise challenge when the drug is

22 added? And specifically, even when Dr. Casaburi gave

1 his two cases, one of them, the 65-year-old was the

2 example of somebody who's having problems but they're

3 on LAMAs. So we don't really have good information on

4 that.

5   DR. DISSE: Thank you for the question. So

6 the exercise studies allowed, had a specific regime

7 allowing co-medication. Dr. Hamilton?

8   DR. HAMILTON: Yeah, so just maybe a

9 clarification on what was allowed in the exercise

10 studies. You're absolutely right, for the exercise

11 studies we did not allow tiotropium. And one of the

12 reasons there was in the design of the studies to

13 optimally be able to understand the relationship

14 between the airflow, improvements in airflow and it's

15 endurance time, we felt that to include tiotropium in

16 those studies would be somewhat counterproductive.

17   We did, however, allow short-acting

18 muscarinic antagonists, so ipratropium was allowed in

19 those studies as maintenance. And we actually had

20 somewhere on the order of 35 percent of patients were

21 on ipratropium. In fact many patients who were on

22 tiotropium coming into the study, they were allowed to

1 switch over to ipratropium, and I think it was around

2 about 40 percent of the patients who were on tio coming

3 into the study switched over to ipratropium.

4   Also xanthines were allowed in inhaled

5 steroids. So the only -- obviously LABAs were

6 restricted as well. So the only -- out of the

7 concomitant therapies, it was tiotropium that was not

8 allowed.

9   DR. JACOBY: Dr. Calhoun?

10   DR. CALHOUN: Thank you. I have a couple of

11 hopefully short and brief questions. The first is

12 related to the fact that in your Phase II data you

13 demonstrated a clear dose response with respect to

14 physiologic outcomes.

15   And in the safety database there appeared to

16 be some differentiation on some safety parameters, 5

17 versus 10, and you're proposing to market 5 micrograms.

18 So the question is how good is the Respimat in

19 producing a 5 microgram dose each time? What's the

20 variability of the dose?

21   DR. DISSE: So the Respimat device is highly

22 reliable. It fulfills all specifications also at very

1 low doses. This has to do with that it is not a powder

2 device, it is a solution device, which means we have

3 solutions of the drugs. Solutions are well defined.

4 And the solution is nebulized and so small droplets are

5 formed.

6   And here, just as an example, slide please,

7 so this of course doesn't explain the precision at low

8 doses, but it gives an idea. So 22 percent remain in

9 the device, but our label dose is based on the ex-

10 mouthpiece device. So then about 40 percent of this,

11 or 50 percent of the label dose go to the lungs.

12   Some 40 percent go to the oropharynx. And as

13 mentioned, generation of droplets is precise. So the

14 precision of the instrument is as good for 5 micrograms

15 as for 10 micrograms, as it would be for 2.5

16 micrograms.

17   DR. CALHOUN: So the coefficient of variation

18 you're showing there is about 32 percent.

19   DR. DISSE: If you have specific questions

20 here to address the pharmaceutical quality, I then

21 would like to invite our expert to explain the

22 specification. Dr. Schmelzer?

 1   DR. CALHOUN: I guess my point is that if the

 2 coefficient of variation is 32 percent, then some

 3 people might get a 2 microgram dose and some people

 4 might get a 10 microgram dose.

 5   DR. DISSE: It is in fact lower and meets the

 6 typical specifications. Dr. Schmelzer, please?

 7   DR. SCHMELZER: I'm Dr. Schmelzer,

 8 pharmaceutical development at Boehringer Ingelheim. In

 9 fact what is shown on these slides is the biological

10 response. Regarding the device itself, it meters very

11 precisely because the system itself overcomes two

12 weaknesses of the powder system and of the pressurized

13 metered dose inhaler.

14   If the powder system has individual filled

15 capsules or blisters, you have a variability of the

16 filling, of the filling mass, and also of the content

17 of the active drug substance. In our case, as Dr.

18 Disse said, we have a reservoir of an aqueous solution

19 which is exactly measured during the dosing.

20   Another weakness of pressurized metered dose

21 inhalers that are driven with propellants is that the

22 composition of the solution or suspension contained in

1 such containers changes over time of use because you

2 get a kind of a concentration. This is also completely

3 overcome with Respimat since the aqueous solution

4 contained in our reservoir does not change, neither

5 over storage time nor over use time.

6   DR. CALHOUN: Okay, thank you. So another

7 question has to do with the concomitant medications.

8 As I understood, you allowed individuals with long-

9 acting muscarinic antagonists, specifically tiotropium,

10 in the trial. And then those who were on LABAs were

11 given the option of switching to ipratropium. Is that

12 right?

13   DR. DISSE: Yeah. Correct.

14   DR. CALHOUN: So given the I guess

15 pharmacologic interaction between ipratropium and

16 tiotropium, that seems a little curious to me. Did you

17 then separate out people who were both on ipratropium

18 and tiotropium?

19   DR. DISSE: It is not that patients were on

20 both, because the label of ipratropium would exclude

21 tiotropium treatment and the reverse. So patients

22 either maintained their tiotropium, and if they were on

1 LABA, they may have switched to ipratropium, but not on

2 both. So this was excluded.

3   DR. CALHOUN: Okay. So those people who were

4 on LABAs who got switched to ipratropium were not on

5 LAMAs. Is that right?

6   DR. DISSE: Correct. Yeah.

7   DR. CALHOUN: Okay. Thank you. And the

8 third and final question has to do with the patient

9 reported outcomes. And I'm a little bit curious as to,

10 in your Slide 47, there was a large placebo effect over

11 the course of 24 months. And so that immediately

12 raises the concern for me that the tool might not be

13 externally valid.

14   DR. DISSE: Dr. Hamilton, that's a question

15 (inaudible - crosstalk).

16   DR. CALHOUN: And in fact you've got a

17 failure to demonstrate symptom improvement in the cycle

18 ergometry in Study 38, showed it in 37 but not in 38.

19 So once again, there's some inconsistency in the tool

20 it seems.

21   DR. HAMILTON: Yeah, I think so. Just to

22 make sure I'm clear on, you said 47, this is correct,

1 the TDI focus score over the 48 weeks, is that correct?

2   DR. CALHOUN: Yes, thanks.

3   DR. HAMILTON: Yeah, so I think what I would

4 like to show is actually from this, as I mentioned, the

5 primary analysis for the TDI was based on the combined

6 dataset from 13 and 14, but we also do have the data

7 for 13 and 14 individually. And if we could bring up

8 the slide showing the TDI over 48 weeks for the 13 and

9 14 separately. Because this -- it was an unexpected

10 placebo response.

11   We've used the TDI in other programs, so for

12 example for the tiotropium program. So we have quite

13 an extensive database on the use of the TDI, and

14 specifically the placebo response. And in general, we

15 have found that when you go from the first measurement

16 time point at 6 weeks up to 48 weeks, you tend to see a

17 relatively stable placebo response.

18   And I think we're bringing this up now, yes.

19 Thank you. So if I could then focus now on the

20 individual studies. And if you look on the right hand

21 side, I think the Study 14, that tends to be the more

22 typical response that we've seen where the placebo

1 response is stable over the 48 weeks. In the 13, you

2 can see that's clearly different where we saw this

3 increase over time. We did perform some post hoc

4 exploratory analyses to see if we could identify the

5 reason for that.

6   One thing we did was to look at pattern

7 mixture modeling, which is a way to try to address the

8 differential discontinuation. And that, and if I could

9 show that, I think we presented this in the briefing

10 document. And when we did that, we did find that this

11 did seem to give us a possible explanation that it was

12 related to some of these patients dropping out earlier

13 and the extrapolation of their data.

14   And this is, I think, the first time we've

15 noticed in all of our studies a placebo response like

16 that, so it was very unusual. But we think it's

17 explained by, to some extent at least, by the

18 differential discontinuation.

19   DR. JACOBY: Thank you.

20   DR. CALHOUN: (Inaudible) the minimal

21 clinical important difference?

22   DR. HAMILTON: Yes, I believe for the TDI it

1   is defined as one unit.

2   DR. JACOBY: Dr. Greenberger?

3   DR. GREENBERGER: A slide was presented

4   earlier with the proposed label, it had two bullet

5   points. One was the pivotal studies and the other was

6   the exercise findings. The reason I bring it up is

7   that I believe the inclusion criteria for the studies

8   were different regarding the LAMAs, like others have

9   brought up. But the pivotal studies included them more

10 often and the exercise did not. But the reader might

11 not know that, is my question.

12   DR. DISSE: You are addressing specifically

13 the exercise part of the label. And your concern is

14 that the co-medication in the exercise part of our

15 studies was different.

16   DR. GREENBERGER: Well, the 14 percent -- I'm

17 happy to see you know improvement, physiologic

18 improvement, but my question was the, in reading that,

19 one might not know that there was a difference in the

20 demographics of your patients, you know, in the

21 studies. And am I wrong, but the exercise were per

22 protocol, so to speak, versus the other's intention to

1 treat.

2   DR. DISSE: Dr. Hamilton?

3   DR. HAMILTON: Yeah, just to make sure I'm

4 clear on the slide that you're speaking to, was it the

5 slide that I presented at the end, and I'm showing it

6 here, Slide CE-62? Are you referring to this specific

7 slide?

8   DR. GREENBERGER: There was an earlier -- I

9 think -- did Dr. Luik show it? I thought I saw a slide

10 on proposed package insert.

11   DR. HAMILTON: Yeah, if I recall correctly,

12 Dr. Luik was presenting the indication.

13   DR. GREENBERGER: Yeah, maybe that was --

14   DR. HAMILTON: Yeah, in our proposed -- so

15 what I've shown here is the specific information we are

16 proposing to include for the exercise. But overall, in

17 our clinical study section, we are providing a, what we

18 believe is a relatively robust description of the

19 population that was included in the pivotal studies.

20   DR. GREENBERGER: Could you point me to the

21 approximate information on let's say SAMAs and LAMAs in

22 the exercise group versus the other studies?

 1   DR. HAMILTON: Yes, I think to your point,

 2 and I think I understand the point, we have not,

 3 currently in our proposed labeling, put any information

 4 specifically on the patient population in the exercise

 5 studies, so that would be correct.

 6   DR. DISSE: So that is certainly also to be

 7 discussed then with the agency. And, as proposed, the

 8 exercise part would be in the clinical trial section

 9 and that would include a description of the population.

10   DR. JACOBY: Dr. Terry?

11   DR. TERRY: The Respimat, it's my

12 understanding was approved in Europe previously. Have

13 there been any problems with the delivery system

14 malfunctioning? Or I've used the device a couple of

15 times and I've gotten the impression it requires, in

16 order to cock it, a certain amount of force. Any

17 problems with people with arthritis for instance being

18 able to use it?

19   DR. DISSE: As with any device, there are

20 certainly a number of complaints reaching the company,

21 but that's at a very low level. I'm not aware of

22 specific complaints that the force was not reached.

1 But I would like to invite again Dr. Schmelzer. She

2 has evaluated the complaints which reach the company

3 concerning the Respimat.

4   DR. SCHMELZER: Thank you. Christel

5 Schmelzer, pharmaceutical development at Boehringer

6 Ingelheim. You have seen that the majority of the

7 patients were in the elder range and we did not get

8 specific complaints that the device was not

9 functioning.

10   In all the pivotal trials, about 50,000

11 Respimat inhalers have been used. We did not get

12 complaint of any destroyed or malfunctioning device.

13 We got about 18, or not about, we got 18 complaints of

14 malfunctioning. These inhalers were returned to us.

15 They were investigated in our laboratories, and not of

16 the described complaint could be confirmed when we

17 inspected these devices.

18   DR. DISSE: So we can certainly not exclude

19 that there may be patients with very specific

20 limitations that would have problems using this device.

21   DR. JACOBY: Mr. Mullins?

22   MR. MULLINS: My question is about the

1 exercise trials and sustainability. How can you make

2 your assumptions about sustainability with the exercise

3 trial if all of the -- if the bike test was completed

4 within two hours of dosing? So that's my concern. My

5 second question is I would like to see a segmentation,

6 or delineation of the comorbidities of the patients

7 involved in the 48-week trial.

8   DR. DISSE: Okay, first question, Dr.

9 Hamilton.

10   DR. HAMILTON: So our primary objective in

11 designing the exercise studies was to be able to

12 evaluate the relationship between the improvements in

13 airflow and how that translated into improvements on

14 the one hand in hyperinflation, where we expect to

15 reduce hyperinflation, and then exercise tolerance.

16   We, as many others who have studied in that

17 area, have felt it necessary, and certainly I guess the

18 state of the art for that is to be looking at the peak

19 bronchodilating effects to be able to do that. So all

20 the studies that I'm aware of on exercise, and I think

21 the FDA had pointed out a few of those studies in their

22 briefing package, they've all measured at two hours

1 post- dose.

2   There is one study that we conducted with

3 tiotropium looking at eight hours post-dose. But in

4 general the reason for the two hours is to give you an

5 optimized bronchodilation so that you can evaluate the

6 relationships between the improved airflow and the

7 exercise tolerance.

8   DR. DISSE: The second part of your question

9 addressed the co-medications, comorbidities. Can I

10 please have this slide from the core presentation? So

11 as depicted here, some 45 percent were inhaled

12 steroids. LABA at baseline was common, but of course

13 not allowed in the study, and to some extent then

14 changed.

15   MR. MULLINS: My question is specifically is

16 for obesity. Since there were many African-Americans

17 that were excluded, that's a serious concern of mine

18 because I still -- I'm not sure why you -- why it's

19 acceptable to have only one percent when many studies

20 show that one of the fastest growing populations within

21 asthmatics, so the asthma population with COPD, are

22 African-American, particularly young African-American.

1 So I wanted to specifically enquire about obesity and

2 that particular comorbidity. So if you have that

3 analysis I'd like to see that since you have a limited

4 number of African- Americans.

5   DR. DISSE: So we have not specifically

6 evaluated for obesity. We did this for

7 pharmacokinetics and exposure, but that probably

8 doesn't address your question. And if your interest is

9 specifically in African-Americans, we have of course

10 evaluated the specific adverse event profile.

11   MR. MULLINS: So you have no data on obesity,

12 the number of patients that were obese in this study?

13   DR. DISSE: We do have this data, but we

14 didn't put them on a slide. So --

15   MR. MULLINS: Yeah, I mean by the nature of

16 COPD, many of the patients cannot exercise or don't

17 exercise so they are obese. So I would think that

18 would be one of the primary comorbidities that you

19 would have statistical evidence so that we can make

20 some evidence based claims, some claims that are

21 relevant to the general population or the broader

22 population. So that's why I'm trying to understand

1 that better, so that I can intelligently analyze the

2 effectiveness of olodaterol.

3   DR. DISSE: So I think I need to discuss with

4 our statisticians how much time it would take to dig

5 out these data.

6   DR. JACOBY: Dr. Connett?

7   DR. CONNETT: The arguments made at the

8 beginning that this would be the first drug that is

9 approved for exercise tolerance, all the comparisons on

10 exercise tolerance seems to be olodaterol versus

11 placebo. But the competing drugs, long-acting beta

12 agonists and tiotropium, why aren't there comparisons

13 of that nature as well in it?

14   DR. DISSE: Do I understand, you're asking

15 whether we have comparisons to other drug classes or

16 drugs?

17   DR. CONNETT: Well, I'm asking why there

18 aren't such comparisons since those would be the

19 competing drugs, this would be the first one that would

20 be approved with some indications for improving

21 exercise tolerance.

22   DR. DISSE: I'm not aware that drugs are

1 approved for exercise tolerance, but certainly other

2 drugs have been studied. Dr. Hamilton, you can comment

3 on the literature.

4   DR. HAMILTON: Maybe one point on what I'm

5 aware of with the literature, I think in terms of

6 monotherapies, I'm aware that those monotherapies have

7 generally compared with placebo, so we have conducted

8 tiotropium studies; that's with placebo.

9   I believe that indacaterol and aclidinium

10 have also conducted their studies versus placebo.

11 There was one study referenced by the FDA, which was

12 where they looked at the combination, so the ICS LABA,

13 Advair, which was looked at both versus placebo plus

14 its individual components. So that is my knowledge of

15 the literature.

16   Maybe just to make one other point, in an

17 ongoing program for our combination program, we are

18 currently conducting studies on exercise tolerance

19 where we are looking at the combination of tiotropium

20 and olodaterol. And within that, we also have the

21 monotherapy, so within that we will be studied

22 tiotropium olodaterol as a secondary analysis.

1   DR. JACOBY: Thank you, committee members,

2 for your questions and thank you for your answers.

3 We've gotten a little bit behind, for which I will

4 share responsibility. We're going to take a 10-minute

5 break and I will restart at 10:37. Committee members,

6 please remember that you're not supposed to talk about

7 this outside of this room.

8   (A recess was taken.)

9   DR. JACOBY: Okay. We'll now proceed

10 with presentations from the FDA. FDA Presentations

11 Overview of the Clinical Program

12   DR. LIM: Good morning. My name is Robert

13 Lim and I'm a medical officer with the FDA in the

14 Division of Pulmonary, Allergy and Rheumatology

15 Products. On behalf of the Division, it is my pleasure

16 to once again welcome you to the FDA campus at White

17 Oak. I would also like to thank Dr. Jacoby and members

18 of the Pulmonary, Allergy Drugs Advisory Committee for

19 being here today to share your expertise.

20   Over the next 90 minutes or so, members of

21 the FDA will walk you through data from the New Drug

22 Application, or NDA, for olodaterol inhalation spray.

1 The objectives for this time are first to discuss the

2 olodaterol efficacy claim for the long-term, once-daily

3 maintenance bronchodilator treatment of airflow

4 obstruction in patients with COPD; second, to discuss

5 the sponsor's proposed exercise claim; and third, to

6 discuss the safety of the product.

7   Here is an outline of the FDA's presentations

8 today. I will begin by providing a brief overview of

9 the olodaterol clinical program. This will be followed

10 by a review of the efficacy data by statistical

11 reviewer, Dr. Abugov. I will then return to the podium

12 to provide a clinical review of the efficacy and safety

13 data, as well as a framework for evaluating the risk

14 benefit profile of the proposed product.

15   The subject of today's discussion is

16 Striverdi Respimat, or olodaterol inhalation spray.

17 Olodaterol is a new molecular entity belonging to the

18 class of drugs known as long-acting beta agonists, or

19 LABAs. It is formulated as a solution and is delivered

20 via the Respimat device.

21   This device, seen in the picture, is

22 currently approved for use in the U.S. with Combivent.

1 The proposed dose is two actuations of 2.5 micrograms

2 administered once-daily for a total daily dose of 5

3 micrograms. And again, the proposed indication is for

4 the long-term, once-daily maintenance bronchodilator

5 treatment of airflow obstruction in patients with COPD.

6   The regulatory history of this program is

7 fairly straightforward. This is a first cycle review.

8 At the first end of Phase II meeting in 2008, the FDA

9 agreed that it was reasonable to take a 5 and 10

10 microgram total daily doses to their Phase III program.

11 However the dosing interval at that time had not been

12 agreed upon.

13   In a request for advice in 2009, the sponsor

14 submitted data from COPD dose regimen trials in support

15 of once-daily dosing. At that time the FDA recommended

16 that dosing and dose regimen be further explored in

17 patients with asthma because the asthma population

18 would allow for more precise dose selection due to

19 their inherent bronchoreactivity. At the 2011 pre-NDA

20 interaction, there were no significant issues.

21   The olodaterol development program has

22 already been described in detail by the sponsor, so my

1 overview will be short. The key efficacy trials in

2 this development program included multiple dose ranging

3 trials in COPD and asthma, four 6-week spirometry

4 trials, four 48-week spirometry trials, and two 6-week

5 exercise tolerance trials. These will be briefly

6 reviewed in the following slides.

7   This slide summarizes the three dose ranging

8 trials in COPD. Note that the trial numbers in this

9 development program all have a prefix 1222. During my

10 presentations, I will verbally refer to the trials by

11 the numbers after the decimal point, though in the

12 tables and in the slides the entire numbers will be

13 used.

14   So Trial 3 evaluated single doses of

15 olodaterol ranging from 2 to 20 micrograms. Trial 5

16 evaluated the same doses given over a four-week

17 treatment period. And Trial 26 evaluated once-daily

18 versus twice-daily dosing comparing the 2 microgram

19 twice-daily to 5 microgram once-daily dose, and the 5

20 microgram twice-daily to the 10 microgram once-daily

21 dose.

22   Note that the 2 microgram twice-daily dose

1 was compared to 5 microgram once-daily, as at the time

2 of this trial there was no 2.5 microgram formulation.

3 In order to give an overview of the dose ranging, I

4 will summarize results from Trials 5 and 26 briefly in

5 the next two slides. For your reference, results from

6 the dose ranging trials are also available in the FDA

7 briefing package.

8   This slide summarizes the results from Trial

9 5. The Y-axis is trough FEV1 following four weeks of

10 treatment, and across the X-axis are the olodaterol

11 doses 2, 5, 10 and 20 micrograms once-daily. Based on

12 the results, based on these results, there was little

13 added benefit to doses greater than 10 micrograms, and

14 at doses less than 5 micrograms the benefit was

15 marginal.

16   This slide summarizes the results from COPD

17 dose regimen Trial 26. The Y-axis is FEV1 and across

18 the X- axis is time since a.m. drug administration at

19 three weeks of treatment. Note that this was a

20 crossover trial and olodaterol dose groups were

21 compared to baseline values. As such, there was no

22 placebo.

1   Compared to baseline, all doses of olodaterol

2   demonstrated improvements in FEV1. Additionally, when

3   comparing twice-daily and once-daily regimens with

4   similar total daily doses, differences between dose

5   regimens were modest. Notably, the 24-hour profile of

6   the 5 microgram once-daily dose, shown in blue, was

7   numerically greater than the 2 microgram twice-daily

8   dose shown in red.

9   Based on the results from the COPD dose

10 ranging and dose regimen trials, it was reasonable for

11 BI to proceed to Phase III with a 5 and 10 microgram

12 once-daily doses.

13   While the COPD dose ranging trials were

14 supportive of the 5 and 10 microgram once-daily dose,

15 BI was asked to explore dose and dose regimen in the

16 asthma population as that would allow for more precise

17 dose selection due to their inherent bronchoreactivity.

18 This is of particular importance for LABA products due

19 to their known dose-related class safety issues.

20   This slide summarizes the four dose ranging

21 trials in patients with asthma. Note that it is only

22 in these trials that patients with asthma were exposed

1 to olodaterol. Trial 4 evaluated single doses

2 of olodaterol ranging from 2 to 20 micrograms. Trial 6

3 evaluated the same doses over a four-week treatment

4 period.

5   Trial 27 evaluated the same doses for a four-

6 week treatment period. However, this trial was a

7 crossover compared to Trial 6, which was a parallel

8 group trial. Trial 29 explored dosing frequency

9 comparing twice-daily and once-daily olodaterol

10 regimens.

11   Overall these data were relatively consistent

12 with the COPD dose ranging data, and demonstrated that

13 the 5 and 10 microgram total daily doses were

14 appropriate to bring to Phase III. The twice-daily

15 regimen also did not offer a large benefit over the

16 once-daily regimen.

17   Based on the totality of the data, we have no

18 issues with the sponsor's dose and dose regimen used in

19 their Phase III program. As such, data from the dose

20 ranging trials will not be further discussed. However,

21 dosing will be revisited in the context of the 5 and 10

22 microgram once-daily dose as used in the Phase III

1 program.

2   This slide summarizes the four trials meant

3 to characterize the 24-hour spirometry curves of

4 olodaterol. All four trials were randomized, double-

5 blind, double- dummy, placebo-controlled, active-

6 controlled crossover trials. Trials 24 and 25 included

7 the active comparator formoterol, and Trials 39 and 40

8 included the active comparator tiotropium. The co-

9 primary endpoints of these trials were FEV1 AUC 0-12

10 hours, and FEV1 AUC 12-24 hours. Dr. Abugov will

11 discuss the results from these trials more in his

12 presentation.

13   This slide summarizes the four 48-week

14 spirometry trials. These were submitted as primary

15 support for efficacy. All four trials were generally

16 similar in design. Trials 11 and 12 were randomized,

17 double-blind, placebo-controlled, parallel group,

18 replicate trials, and each trial included approximately

19 600 patients. Trials 13 and 14 were also replicate

20 trials. However, these included the active comparator

21 formoterol and a double-dummy placebo. Each of Trials

22 13 and 14 included approximately 900 patients.

1   This slide summarizes the key similarities

2 and differences between Trials 11 and 12 versus 13 and

3 14. In all four trials non-LABA maintenance COPD

4 medications were allowed during the treatment periods.

5 This included long-acting anticholinergic agents,

6 methylxanthines and corticosteroids.

7   The spirometric co-primary endpoints were

8 also the same between trials and were FEV1 AUC 0-3

9 hours and trough FEV1. However, in Trials 11 and 12,

10 the spirometric co-primary endpoints were assessed at

11 12 weeks compared to 24 weeks in Trials 13 and 14.

12   Trials 13 and 14 also included an additional

13 co- primary endpoint of transitional dyspnea index. It

14 should also be noted that the statistical analysis

15 plans for Trials 11 and 12 were amended post hoc,

16 whereas this was not the case in Trials 13 and 14. Dr.

17 Abugov will discuss this issue more in his

18 presentation.

19   This slide summarizes the two replicate

20 exercise tolerance trials. Trials 37 and 38 were

21 randomized, double-blind, placebo-controlled crossover

22 trials with 6- week treatment periods exploring the 5

1 and 10 microgram once-daily olodaterol doses. Each

2 trial included approximately 150 patients. The

3 endpoints pertinent to today's discussion include

4 endurance time and inspiratory capacity. The endpoints

5 will be discussed in more depth in the third FDA

6 presentation in the discussion of clinical

7 significance.

8   This concludes my brief overview of the

9 olodaterol development program. Dr. Abugov will now

10 present the statistical review of efficacy. Statistical

11 Review of Efficacy

12   DR. ABUGOV: Thank you, Dr. Lim. Good

13 morning everyone. We'll cover the three sets of Phase

14 III trials conducted by the applicant: four parallel

15 arm, 48-week spirometry trials, four crossover

16 spirometry trials with periods six weeks in length, and

17 two crossover exercise tolerance trials with periods

18 six weeks in length. Then we'll discuss subgroup

19 analyses and wrap things up with a summary.

20   The 48-week spirometry trials provide

21 efficacy data which may provide the basis for a

22 decision concerning approval. They include, as primary

1 endpoints, trough FEV1 and FEV AUC 0-3 hours. These

2 trials also include the secondary endpoints SGRQ and

3 incidence of COPD exacerbations.

4   The 6-week spirometry trials attempt to

5 characterize the time profile of olodaterol's effects

6 on FEV1 from 12 to 24 hours after daily administration.

7 The 6-week exercise tolerance trials characterize

8 exercise tolerance time as well as inspiratory capacity

9 six weeks after initiation of treatment.

10   First, the 48-week spirometry studies. As

11 already discussed by the applicant and Dr. Lim, Phase

12 III of this submission includes, for assessment of

13 respiratory endpoints, four parallel arm, 48-week

14 spirometry studies. They occur in two pairs of similar

15 trials.

16   Studies 13 and 14 were designed for European

17 registration, and they include randomization to a

18 European version of formoterol, not approved for use in

19 the United States. Therefore, Studies 13 and 14 could

20 not enroll any patients from the United States.

21 Studies 11 and 12 then were conducted to include

22 patients from the United States without the European

1 formoterol arm.

2   Because only Studies 11 and 12 included

3 patients from United States, the applicant designated

4 those studies as the pivotal trials for evaluation for

5 efficacy in this country. However, when evaluating

6 whether to approve a drug, the agency does not

7 subscribe to the concept of pivotal trials and instead

8 considers all available data.

9   Nevertheless, to control Type 1 error,

10 endpoints to be evaluated for approval must be clearly

11 defined before the data is examined, and we therefore

12 consider the preplanned endpoints of Studies 11 and 12

13 at week 12 primary for evaluation of efficacy.

14   Mixed model repeated measurements,

15 abbreviated as MMRM, was applied to the collected data.

16 All of the MMRM included fixed effects treatment, day,

17 tiotropium strata, baseline and treatment by day, and

18 baseline by day, as well as random effects of patient.

19   The preplanned model for Studies 11 and 12

20 also included as fixed effects interaction of

21 tiotropium with treatment, day and treatment by day.

22 Data missing between time points was imputed using

1 least favorable observation carried forward.

2   As a final note, database locks for all pairs

3 of trials in this submission occurred in the time

4 sequence corresponding to trial numbers. For example,

5 the locks for Trials 11 and 12 occurred before those

6 for Trials 13 and 14. This enabled the applicant to

7 apply learnings from earlier pairs of trials to help

8 design statistical models for later pairs of trials.

9   Studies 11 and 12 used a hierarchical

10 approach to control Type 1 error for the primary

11 endpoints in the order shown, with effectiveness for

12 olodaterol 10 micrograms established for each primary

13 endpoint before examining the effectiveness of

14 olodaterol 5. Planned endpoints for the secondary

15 endpoints, SGRQ, or planned analyses, in Studies 13 and

16 14, in moderate exacerbations in Studies 11, 12, 13 and

17 14 were also hierarchically ordered, however they were

18 on data merged over all available studies.

19   In this review, corresponding to how the

20 agency examines secondary endpoints for efficacy, they

21 were analyzed separately for each study with testing of

22 exacerbations following SGRQ in the hierarchy as

1 planned by the applicant. Change in AUC 0-12 hours was

2 not included in the hierarchy, therefore any

3 significance test in this endpoint should be considered

4 only nominal, not representing the true probability of

5 Type 1 error.

6   In Studies 11 and 12, the statistical models

7 provided in this submission did not correspond to those

8 preplanned in the protocol, with the circled

9 interaction terms involving tiotropium deleted. We

10 consider such post hoc changes from preplanned

11 statistical models inappropriate for evaluation of

12 efficacy in confirmatory trials.

13   First, and most important, Type 1 error

14 cannot be controlled, or even calculated, when

15 conducting multiple unplanned statistical tests.

16 Second, compared to the preplanned model, the

17 applicant's post hoc model down weights patients

18 taking tiotropium, a down weighting based on a

19 tenuous assumption that tiotropium use reduces the

20 effect of olodaterol, an assumption which, as we shall

21 see, is not supported by the available evidence.

22   Let's now begin looking at the results. As

1 mentioned by earlier speakers, the study treatments

2 were given in addition to standard of care. In all

3 four studies, roughly 25 percent of the patients were

4 treated with systemic steroids, and 50 percent took

5 inhaled steroids.

6   Approximately 20 to 30 percent took

7 xanthines, short-acting, or long-acting

8 anticholinergics. Twenty- four to 29 percent of the

9 patients in Studies 11 and 12 were not treated with

10 COPD medications, compared to 19 percent of the

11 patients in Study 13 and 14.

12   All of the 48-week spirometry studies showed

13 mean trough FEV1 numerically favoring olodaterol over

14 placebo. In Studies 11, 13 and 14, the two-sided 95

15 percent confidence intervals, for the difference

16 between olodaterol 5 and placebo, don't cross zero.

17 That is to say the difference between the olodaterol 5

18 and placebo for trough FEV1 is statistically

19 significant at the 0.05 level.

20   In Study 12, however, the confidence interval

21 does cross zero and so the difference between

22 olodaterol 5 and placebo for Study 12 is not

1 statistically significant. On the average, over these

2 studies, treatment with olodaterol 5 increased trough

3 FEV1 by 65 milliliters.

4   We had some concerns around the use of MMRM.

5 First, missing data was imputed by carrying forward

6 earlier observations which, when used with MMRM, may

7 distort the covariance matrices used to calculate

8 confidence intervals.

9   However, a sensitivity analysis, with

10 observed data only, yielded results within 4

11 milliliters of the analysis with data carried forward,

12 alleviating our concerns. Second, because MMRM depends

13 on the assumption that data is missing only at random,

14 such models may not reflect what actually happens in

15 the target population. This second concern is

16 alleviated somewhat because the percent of data missing

17 at week 12 was less than 10 percent.

18   Confidence intervals for the difference

19 between olodaterol 10 and 5 for week 12, trough FEV1,

20 overlap zero for all studies, suggesting that the

21 higher dose, olodaterol 10, is not more effective than

22 the lower dose, olodaterol 5.

1   For Studies 11 and 12, the applicant

2 attempted to replace the preplanned model with one

3 designated post hoc, which inflated the estimated

4 benefit of olodaterol. We've already discussed the

5 reasons for our concern with models designed after

6 examining the data and shall now address the underlying

7 assumption in the post hoc model that tiotropium

8 reduces the effect of olodaterol.

9   From Studies 11 and 12, the applicant argued

10 that because patients taking tiotropium had a

11 numerically smaller response than those not taking

12 tiotropium, the preplanned statistical model, which

13 gives patients taking tiotropium equal weight in the

14 results, is incorrect.

15   Because such patients are only a minority in

16 these studies, the applicant argued that the model

17 should be corrected to reflect this fact. However,

18 there are other studies available in this submission

19 which can be used to confirm or reject this post hoc

20 argument.

21   In particular, and in contrast to the

22 argument derived from Studies 11 and 12, olodaterol 5

1   in Studies 13, 14 and 25 had a numerically greater

2   effect on patients taking tiotropium compared to

3   patients not taking tiotropium. Study 25, on the other

4   hand, shows a result similar to that for Studies 11 and

5   12.

6   So, all in all, three studies show a larger

7   effect of olodaterol in the presence of tiotropium, and

8   three show a smaller effect. Overall, there is no

9   consistent evidence that tiotropium affects

10 olodaterol's impact on FEV1. And there is no evidence

11 which even vaguely suggests that the preplanned model

12 needed to be changed.

13   We can now discuss change in AUC 0-3 hours.

14 Results from the preplanned statistical model show

15 olodaterol 5 with a statistically significant effect

16 compared to placebo on week 12 AUC 0-3 in all four

17 parallel arm crossover trials, with an average effect

18 equal to 155 mls.

19   Those are parallel arm trials, not parallel

20 arm crossover trials. I just noticed a typo.

21 Confidence intervals for the difference between

22 olodaterol 10 and 5 for week 12 AUC 0-3 hours overlap

1 zero for all three studies, suggesting, as for trough

2 FEV1, that olodaterol 10 is not more effective than

3 olodaterol 5.

4   We can now move on to the secondary

5 endpoints. Change from baseline AUC 0-12 was modeled

6 without plans to control Type 1 error in the face of

7 multiple endpoints. Having said that, in Studies 11

8 and 12, the difference between olodaterol 5 and placebo

9 for change from baseline AUC 0-12 at week 12, was

10 nominally statistically significant with an average

11 effect of 122 mls.

12   As in the primary endpoints, confidence

13 intervals for the difference between olodaterol 10 and

14 5 overlap zero for both studies, suggesting again that

15 olodaterol 10 is not more effective than olodaterol 5.

16 There was no demonstrated effect of olodaterol 5 on

17 incidence of moderate exacerbations, those requiring

18 administration of antibiotics or systemic steroids

19 without hospitalization.

20   Two of the parallel arm trials examine the

21 effect compared to placebo of olodaterol and SGRQ. The

22 effect of olodaterol 5 was significant in Study 14,

1 with a benefit of 3.15, which is below the 4.0 value

2 considered medically relevant.

3   So in the 48-week spirometry trials, we've

4 seen that, compared to placebo, olodaterol 5 had

5 significant effects on trough FEV1 and AUC 0-3, with

6 average effects equal to 65 mls for trough FEV1 and 155

7 mls for AUC 0-3. Giving patients a higher dose of

8 olodaterol did not provide greater benefits.

9   Olodaterol 5 provided a nominally significant

10 benefit on AUC 0-12, with an average effect of 122 mls.

11 There was a statistically significant effect on SGRQ,

12 but in only one of two studies with an effect size less

13 than that considered clinically meaningful. There was

14 no statistically significant effect of olodaterol on

15 the incidence of moderate exacerbations.

16   Let's now move on to the four 6-week

17 spirometry trials. MMRM was applied to data from

18 crossover Studies 24 and 25 with fixed effects

19 including treatment, center and period, with random

20 effect patient nested within center. Change in

21 respiratory variables were based on changes from study

22 baseline.

1   A hierarchical approach was used to control

2 Type 1 error for the primary endpoints with

3 effectiveness for olodaterol 10 established for week 6

4 AUC 0-12 and AUC 12- 24 respectively before examining

5 statistical significance of olodaterol 5. Modeling of

6 crossover Studies 39 and 40 was similar to that of

7 Studies 24 and 25, except that center was not included

8 in the model and baseline was included.

9   An issue in these studies is that they

10 measure effects of olodaterol on FEV during the latter

11 half of the day. However, there are two issues here.

12 First, we only have data during the latter half of each

13 day for week 6 rather than at later time points

14 preferred by the agency for evaluation of efficacy,

15 such as week 12 in the parallel arm trials. And

16 second, even at week 6, there are significant gaps in

17 the data.

18   Statistically significant benefits of

19 olodaterol were seen for AUC 12-24 at six weeks in all

20 of these four studies. The effect of olodaterol on AUC

21 0-24 at six weeks was nominally significant in all four

22 of the crossover studies, as you might expect, since

1 AUC 0-24 is really a composite of statistically

2 significant effects on AUC 0-12 and AUC 12-24.

3   For crossover Trials 24 and 25, there was a

4 large gap in the data from hours 14 to 23 after

5 administration. The two black lines are the two doses

6 of olodaterol, the green line is the placebo, and the

7 red line is formoterol. In the middle of the graph you

8 can see a jump in the red formoterol line because it's

9 administered twice daily.

10   As seen in the earlier presentations, the two

11 doses of olodaterol show very similar effects. The 24-

12 hour dose graph shown earlier by Dr. Lim, and the other

13 graph shown by the applicant, don't show the data gap.

14 It's hidden by a straight line between data points.

15 That use of a straight line however, ignores any

16 diurnal patterns in FEV1. Similarly, for crossover

17 Trials 39 and 40, there's a data gap from hours 12 to

18 22 after administration.

19   In this graph, as before, the two black lines

20 are doses of olodaterol and the green line is for

21 placebo. As in the dose ranging trials, the two doses

22 of olodaterol again have similar effects. The red line

1 is tiotropium, which is administered once daily and

2 seems to have an effect similar to that of olodaterol.

3 Again, the graphs show a data gap, ignoring potential

4 diurnal patterns in FEV1.

5   In summary, compared to placebo, olodaterol 5

6 has a statistically significant effect on AUC 12-24.

7 However, because of gaps in the data, the

8 quantification of its effect was imprecise.

9   We'll now shift gears to discuss the two

10 crossover studies examining exercise tolerance.

11 Crossover Studies 37 and 38, to examine exercise

12 endpoints, were analyzed using MMRM. Fixed effects

13 included treatment, baseline and period with random

14 patient effects. Change in respiratory variables were

15 based on changes from study baseline. Neither of these

16 studies included patients from the United States.

17   A hierarchical approach was used to control

18 Type 1 error over the primary endpoint in IC at

19 isotime, with olodaterol 10 established as significant

20 before analyzing effectiveness of olodaterol 5. If the

21 primary endpoint was statistically significant for both

22 studies, the secondary endpoint, IC at isotime and then

1 breathing discomfort were tested. Let's now look at

2 the results.

3   Compared to placebo, olodaterol 5 provided a

4 statistically significant benefit to exercise

5 intolerance. The average increase in endurance time

6 was 47 seconds. In Study 37, the 51 second increase in

7 exercise endurance due to olodaterol added 14 percent

8 to the 370 second placebo endurance time.

9   In Study 38, the 42 second increase added 12

10 percent to the 396 second placebo endurance time. In

11 both exercise trials, olodaterol provided statistically

12 significant benefits to inspiratory capacity at

13 isotime. The average benefit was 130 milliliters.

14   To summarize the exercise endurance studies,

15 compared to placebo, olodaterol 5 had statistically

16 significant effects on exercise endurance in IC at

17 isotime.

18   Models with subgroup by treatment

19 interactions were used to gauge the effects on

20 olodaterol's benefit to FEV1 of race, country of origin

21 and age. These analyses were done separately for each

22 study. Those analyses did not reveal any race or

1 resident specific differences in the efficacy of

2 olodaterol.

3 However, younger individuals seemed to

4 benefit more from administration of olodaterol than

5 older individuals. The age specific difference in

6 effect is not especially surprising given natural

7 reductions in lung capacity with age and the

8 progressive damage due to lung tissue associated with

9 COPD.

10 In summary, this submission did demonstrate

11 benefits of olodaterol to pulmonary function. Four

12 randomized, parallel arm trials showed that olodaterol

13 5, as an add-on to standard of care, without other

14 LABA, provided statistically significant benefits to

15 the primary endpoints, week 12 change from baseline

16 trough FEV1 and FEV1 AUC 0-3 hours.

17 Nominally statistically significant benefit

18 to the secondary endpoint, week 12 change from baseline

19 AUC 0-12 was also demonstrated. We also saw

20 statistically significant effects of olodaterol on week

21 6 AUC 12-24 and AUC 0-24. However, due to gaps in the

22 data, good quantitative estimates in the improvements

1 for these endpoints were not available.

2   A statistically significant difference in

3 SGRQ between olodaterol 5 and placebo was seen in one

4 of two parallel arm studies. In that study, the

5 reduction compared to placebo was 3.15, which is less

6 than the 4.0 threshold considered clinically

7 significant. No statistically significant effects were

8 seen on COPD exacerbation rate.

9   Statistically significant benefits of

10 olodaterol 5 were seen in two crossover studies for

11 week 6 exercise endurance in IC and isotime. As a

12 final note, no statistically significant differences

13 were seen between olodaterol 5 and olodaterol 10.

14 Thank you for your attention. Clinical Review of

15 Efficacy, Safety, Risk/Benefit

16   DR. LIM: Thank you, Dr. Abugov. I will be

17 giving the third FDA presentation. The goal of this

18 time is to provide a clinical review of the olodaterol

19 efficacy and safety data and to provide a framework for

20 evaluating the risk benefit profile of the proposed

21 product.

22   This slide outlines the structure of this

1 presentation. I will first summarize the efficacy data

2 with respect to bronchodilation and then discuss the

3 efficacy data with respect to exercise tolerance. This

4 will be followed by a presentation of the safety data

5 and will conclude with a framework for a risk benefit

6 assessment.

7   As a reminder, there were four 48-week

8 spirometry trials that served as primary evidence for

9 efficacy for bronchodilation. These are summarized in

10 this table. Based on the results from these trials,

11 the treatment effect of olodaterol 5 micrograms at 12

12 weeks with regard to trough FEV1 was 65 milliliters,

13 with a range of 33 to 84 milliliters across trials.

14 With regard to FEV1 AUC 0-3 hours, the treatment effect

15 was 155 milliliters with a range of 134 to 178

16 milliliters, again at 12 weeks.

17   Using the protocol specified analysis, these

18 results were statistically significant in three out of

19 the four 48-week spirometry trials. There was also no

20 incremental benefit of the 10 microgram dose above the

21 5 microgram dose. It should also be noted that in

22 these trials, except for LABAs, COPD maintenance

 1 medications were allowed during the entire treatment

 2 period.

 3   I will now review the pertinent results from

 4 the exercise tolerance trials. As a reminder, there

 5 were two trials that served as primary support for

 6 exercise tolerance, which are summarized in this table.

 7 Results from Trials 37 and 38 are summarized here. In

 8 both trials, olodaterol 5 micrograms improved endurance

 9 time by 12 to 14 percent, or 42 to 51 seconds compared

10 to placebo. This was statistically significant.

11   With regard at inspiratory capacity and

12 isotime, the improvement from placebo ranged from 84 to

13 182 milliliters. And as with the endurance time, was

14 also statistically significant. Although the endurance

15 time and inspiratory capacity were statistically

16 significantly improved following the treatment, it is

17 unclear if these findings were clinical meaningful.

18   In order to better evaluate the potential

19 clinical significance of these findings, I will briefly

20 review how the sponsor assessed endurance time as well

21 as lung volumes as it pertained to exercise tolerance.

22 I'll also highlight three specific issues that may

1 affect interpretation of clinical significance.

2   The sponsor used cardiopulmonary exercise

3 testing to evaluate endurance time. This testing is

4 designed to assess a patient's integrated response to

5 intense physical stress. During testing, the patients

6 engage in intense physical activity until they reach

7 symptom limitation. During this time, multiple

8 parameters are monitored which assess patient response.

9   Per American Thoracic Society guidelines, the

10 preferred equipment for exercise testing is a cycle

11 ergometer. This was used by the sponsor. Although

12 this is the preferred method, it should be noted that

13 not all patients can ride an exercise bike for reasons

14 entirely separate from the exercise tolerance, such as

15 arthritis, orthopedic injuries and morbid obesity.

16   There are two types of exercise protocols,

17 maximal incremental protocols and constant work rate

18 protocols. In maximal incremental protocols, patients

19 are subject to increasing work rates until they reach

20 exhaustion. In constant work rate protocols, patients

21 perform at a set work rate until exhaustion. The set

22 work rate is usually determined during previously

1 performed incremental testing.

2   In the sponsor's exercise tolerance trials,

3 they used an incremental protocol prior to study drug

4 administration to determine maximal work capacity. The

5 patients then performed constant work rate cycle

6 ergometry testing at 75 percent of that maximal

7 capacity. The time to symptom limitation during this

8 testing was defined as endurance time.

9   This testing was performed once prior to the

10 treatment period to familiarize a patient to the

11 testing procedure, once at baseline, and then following

12 each 6- week treatment period.

13   In COPD, reasons for exercise limitation

14 during exercise testing are multifactorial. However,

15 it is generally accepted that increased hyperinflation

16 plays a key role. In flow-limited COPD patients, the

17 expiratory time is not sufficient for a complete

18 expiration during quiet breathing.

19   This leads to chronic hyperinflation at rest,

20 which manifests as decreased inspiratory capacity and

21 increased functional residual capacity. Inspiratory

22 capacity and functional residual capacity are boxed in

170

1 red in the cartoon on the right.

2   During exercise, due to increased ventilatory

3 demand hyperinflation dynamically increases. This

4 dynamic hyperinflation can be assessed during exercise

5 by measuring inspiratory capacity, which is what the

6 sponsor did. In their exercise tolerance trials, the

7 sponsor assessed for dynamic hyperinflation by

8 measuring inspiratory capacity at isotime.

9   Although it is generally accepted that lung

10 hyperinflation plays an important role in exertional

11 dyspnea and exercise limitation, exactly what change in

12 inspiratory capacity represents a clinically

13 significant improvement in the setting of a clinical

14 trial is not clear. The same is true for endurance

15 time.

16   Given the nature of exercise tolerance

17 testing and the trial design, there are several issues

18 that the FDA has identified which may affect data

19 interpretation. These are generalizability, lack of a

20 minimum clinically important difference, or MCID, and

21 timing. Now I'll discuss each of these potential

22 issues in turn.

1   In order to enter the trials, patients had to

2   be able to perform exercise testing using a cycle

3   ergometer. As such, these patients may not have been

4   fully representative of the COPD population. There are

5   multiple reasons why a patient may be unable to perform

6   cycle ergometry, some of which are listed here.

7   In addition, patients who had limited

8   exercise tolerance for reasons other than exertional

9   dyspnea and fatigue were also excluded from the

10   sponsor's trials. Examples of reasons provided in the

11   sponsor's protocol are listed, and they include morbid

12   obesity, claudication, and angina pectoris. Given

13   these exclusions, it is unclear if the results are

14   generalizable to the broad COPD population.

15   A second issue with exercise testing is the

16   lack of an established MCID in the setting of a

17   pharmacologic intervention. However, researchers have

18   attempted to identify MCIDs following pulmonary

19   rehabilitation.

20   In a study by Puente-Maestu, et al, COPD

21   patients underwent pulmonary rehab for eight weeks,

22   followed by constant work rate cycle ergometry at 75

1 percent maximal workload. Patients also rated

2 perceived exercise tolerance. Study results

3 demonstrated that for a patient to report perceived

4 exercise tolerance as, quote, slightly better, endurance

5 time had to improve by 34 percent, or 101 seconds with

6 a 95 percent confidence interval of 86 to 116 seconds.

7   Laviolette, et al demonstrated similar

8 results. In that study, COPD patients underwent a 6 to

9 12 week pulmonary rehabilitation program followed by

10 constant work rate cycle ergometry performed at 80

11 percent maximal workload. This study demonstrated that

12 in order for a patient to have an improvement in SGRQ

13 of greater than or equal to four, an improvement in

14 endurance time of 153 seconds with a 95 percent

15 confidence interval of 93 to 213 seconds was required.

16 However, one should note that while MCIDs have been

17 generated, they are not universally accepted, nor have

18 they been validated for use in drug development.

19   This slide compares the results from the

20 sponsor's exercise tolerance trials to the literature

21 studies. In comparison to the literature studies, the

22 40 to 50 second improvement seen in the exercise

1 tolerance trials appears modest. However, it should be

2 noted that it is not clear if an MCID generated from a

3 pulmonary rehabilitation program is applicable to a

4 drug intervention trial with a bronchodilator.

5   It should also be noted that while no

6 bronchodilators carry a claim for improved endurance

7 time, investigators have published studies looking at

8 changes in endurance time following treatment with a

9 bronchodilator. The data from these trials have not

10 been reviewed by the FDA, however in general

11 improvements observed in the literature data were

12 greater than 100 seconds. It should also be noted that

13 similar to endurance time, there is also no agreed upon

14 MCID for inspiratory capacity in the setting of drug

15 development.

16   The third issue with the sponsor's exercise

17 tolerance trials is timing. This is perhaps the most

18 important of the three issues. Given that COPD is a

19 chronic disease, trials should be designed to

20 demonstrate a sustained effect over time. The

21 sponsor's trials only included a six-week treatment

22 period. It is unclear if improvements in endurance

1 time and inspiratory capacity, demonstrated after six

2 weeks of therapy, would be durable over the long term,

3 and further, if a six-week exposure is sufficient to

4 fully characterize the treatment effect.

5   For reference, per FDA's COPD guidance

6 documents, for an airflow obstruction indication,

7 trials with a treatment period of at least three months

8 are recommended. For claims related to symptom relief,

9 trials with a duration of at least six months are

10 recommended. And for claims relating to prevention of

11 exacerbation, trials of at least 12 months are recommended.

12   An additional issue with timing pertains to

13 when the assessments were performed. Exercise testing

14 was performed two hours after the morning dose, near

15 olodaterol peak effect. It is unclear if the

16 statistically significant improvements in endurance

17 time and inspiratory capacity would have been

18 maintained had the testing been done later in the

19 dosing interval. This is of particular importance as

20 this is a maintenance medication with proposed once-

21 daily dosing.

22   Although there were statistically significant

1 improvements in endurance time and inspiratory capacity

2 at isotime, due to the reviewed issues, and possibly

3 others, whether or not these improvements are

4 clinically significant is unclear. It should also be

5 noted that no COPD medication carries a claim for

6 improving exercise tolerance and hyperinflation. As

7 such there is no set regulatory pathway.

8   While we recognize that improvements in

9 exercise tolerance and hyperinflation are clinically

10 meaningful, at this time it is unclear how to best

11 integrate these parameters into a regulatory framework.

12 We ask that this afternoon the AC members not only

13 discuss whether or not the findings from the exercise

14 tolerance trials are clinical meaningful, but also to

15 discuss how trials may be best designed to demonstrate

16 clinically meaningful improvements.

17   I will now shift gears to provide a review of

18 the olodaterol safety data, as well as provide a

19 framework for evaluating the risk benefit profile of

20 the proposed product. This slide provides an outline

21 of this portion of the presentation. I'll begin with a

22 summary of safety concerns relevant to the LABA drug

 1 class.

 2   I will then present data regarding the extent

 3 of exposure to the proposed product, which will be

 4 followed by a presentation of the main safety results,

 5 specifically deaths, serious adverse events, common

 6 adverse events, respiratory adverse events, cardiac

 7 adverse events, and neoplasm. Finally, I'll conclude

 8 by providing a framework for evaluating the risk benefit

 9 profile of olodaterol.

10   It should be noted that there are specific

11 asthma-related LABA safety concerns. LABAs have been

12 associated with increased risk of severe exacerbations

13 and asthma deaths. This has led to boxed warnings and

14 medication guides for all LABAs.

15   LABAs are also contraindicated for use IN

16 ASTHMA without another asthma control medication. And

17 sponsors of LABA products with asthma indications are

18 also being required to perform large safety trials.

19 However, it should be noted that no such safety signal

20 has been seen in the COPD population.

21   In this development program, 3,353 patients

22 with COPD were exposed to olodaterol. Of these, 2,334

1 were exposed in parallel group trials, and 1,019 were

2 exposed in crossover trials. The majority of the COPD

3 exposure came from the 48-week spirometry trials. As

4 these trials were the largest with the longest exposure

5 times, they served as the primary safety database.

6   As a reminder, the 48-week spirometry trials

7 are summarized here. Approximately 400 to 450 patients

8 were exposed to at least one dose of olodaterol in each

9 trial. The extent of exposure for these trials is

10 summarized in this slide. A total of 1,759 patients

11 were exposed to either a 5 or 10 micrograms of

12 olodaterol. Approximately 1,590 patients were exposed

13 for at least six months, and 1,114 for greater than 48

14 weeks. The extent of exposure in this program is

15 adequate to allow for assessment of safety.

16   There were a total of 76 deaths in the 48-

17 week spirometry trials. Fifty-three deaths occurred on

18 treatment as defined as within 12 days of the last dose

19 of trial medication. An additional 21 deaths were

20 reported at vital status follow-up.

21   Vital status follow-up was performed at 50

22 weeks for all patients, including those that

1 discontinued the trial early. An additional two deaths

2 were reported after vital status follow-up. As there

3 were no significant differences in deaths that occurred

4 on treatment versus not on treatment, this review will

5 focus on on-treatment deaths only.

6   This table summarizes on-treatment

7 adjudicated deaths. Events that occurred only in the

8 formoterol or placebo groups were not included on this

9 list. Overall deaths were balanced between groups.

10 The most common cause of death was COPD exacerbation.

11   Cardiac-related deaths were no more common in

12 the olodaterol groups compared to placebo. However,

13 deaths due to lung cancer occurred only in the

14 olodaterol groups and not in placebo. Also of

15 interest, pneumonia deaths occurred only in the

16 olodaterol 10 microgram dose group, though the numbers

17 were small.

18   Given the nature of the patient population,

19 the distribution and causes of death were not

20 unexpected. Note that the non-adjudicated analysis of

21 death did not reveal any other imbalances.

22   This table summarizes serious adverse events,

1 or SAEs, that occurred in greater than 0.2 percent of

2 total patients. The most common SAEs were COPD,

3 pneumonia, and atrial fibrillation. Both pneumonia and

4 atrial fibrillation were slightly more frequent in

5 olodaterol groups compared to placebo. However, the

6 overall numbers were relatively small, and overall the

7 SAEs were relatively well-balanced.

8   This table summarizes treatment emergent

9 adverse events that occurred in greater than three

10 percent of patients by treatment, and were more common

11 in at least one olodaterol group compared to placebo.

12 Treatment emergent was defined as occurring within 12

13 days of the last dose.

14   Overall, these were well-balanced. The most

15 common treatment emergent adverse events were COPD,

16 nasopharyngitis and upper respiratory tract infection.

17 While there were some mild imbalances, no AEs

18 demonstrated a dose response and the reported TEAEs are

19 fairly typical for COPD trials.

20   In addition to standard safety analysis, the

21 sponsor also performed additional analyses of

22 respiratory events. These included an analysis based

1 on sponsor- defined pharmacovigilance endpoints, which

2 consisted of preferred terms, or PTs, grouped by

3 similar concepts that did not necessarily correspond to

4 MedDRA system organ class or high level grouping terms.

5   They also performed an adjudicated analysis

6 of SAEs specifically evaluating for respiratory related

7 events. The database for this analysis included all

8 trials with treatment duration of greater than seven

9 days, and all safety data from parallel group trials

10 were included, as was safety data from the first

11 treatment period in crossover trials. Analysis was

12 performed in the total population and separately in the

13 COPD and asthma populations.

14   The pharmacovigilance analysis was consistent

15 with the SAE and treatment emergent adverse event

16 analysis. The adjudicated analysis in the COPD

17 population was also consistent with previous analyses.

18 The asthma population in the adjudicated analysis

19 consisted of 512 patients exposed to olodaterol.

20   These patients came from the asthma dose

21 ranging trials. No patients with asthma were exposed

22 to olodaterol in Phase III. In the asthma population,

1 there was a single respiratory related hospitalization,

2 and there were no deaths, nor intubations.

3   The sponsor's assessment of cardiac safety

4 included an analysis of major adverse cardiac events,

5 commonly referred to as MACE. The MACE events were

6 defined as a cardiac disorder death, a vascular

7 disorder death, any event in the standard MedDRA query,

8 or SMQ, ischemic heart disease sub-SMQ myocardial

9 infarction, and any event in the BI defined stroke

10 pharmacovigilance endpoint.

11   The preferred term sudden death, cardiac

12 death and sudden cardiac death were also included in

13 the MACE definition. In addition to the MACE analysis,

14 the sponsor also conducted an analysis of cardiac

15 adverse events based on standard MedDRA queries, or

16 SMQs.

17   The results of the MACE analysis are provided

18 in this table. This analysis did not reveal any

19 significant imbalances between olodaterol groups and

20 placebo. The results for fatal MACE events, which are

21 not shown, also did not reveal any imbalances.

22   The results of the cardiac SMQ analysis is

1 provided in this table. SMQs included in this table

2 occurred more frequently in at least one olodaterol

3 dose group compared to placebo. Although there were

4 some imbalances, there were no clearly dose-related

5 effects, and the overall number of events were

6 generally small.

7   During review of this application, an

8 imbalance was noted under the SOC neoplasm benign,

9 malignant and unspecified. This table summarizes total

10 AEs, deaths and SAEs that were reported under this SOC.

11 Across these parameters there was an imbalance with

12 events occurring more frequently in the olodaterol

13 groups compared to placebo.

14   This was not driven by a single preferred

15 term, however for deaths and SAEs imbalances were most

16 notable in lung-related neoplasms. As such, lung-

17 related preferred terms are also listed in this table

18 under deaths and SAEs.

19   The data appear fairly consistent with events

20 being most frequent in olodaterol 10 microgram group,

21 followed by olodaterol 5 micrograms. The placebo group

22 reported the fewest events. However it should be noted

1 that in the olodaterol 10 microgram groups, two cases

2 of the lung-related neoplasms presented with multiple

3 metastases, both within 130 days of study drug

4 initiation, and one was reported within seven days of

5 study drug initiation.

6   Additionally, one case in the olodaterol 5

7 microgram group was noted on an annual CT for a stable

8 lung nodule. As such, while an imbalance has been

9 noted, it is of unclear significance.

10   Having had an opportunity to review the key

11 efficacy and safety data for the olodaterol clinical

12 program, I will now end with some comments aimed at

13 providing a framework for evaluating the risk benefit

14 profile of the proposed product.

15   Focusing first on benefit, the olodaterol

16 clinical development program has provided evidence of a

17 bronchodilatory effect based on the replicate 48-week

18 spirometry trials. The mean treatment effect across

19 trials for trough FEV1 was 65 milliliters, and for FEV1

20 AUC 0-3 it was 155 milliliters.

21   Both of these were at 12 weeks. The

22 bronchodilatory effect was further supported by other

1 spirometric endpoints in those trials. The 10

2 microgram once-daily dose also did not offer an

3 incremental benefit above the 5 microgram once-daily

4 dose. In considering the clinical significance of the

5 treatment effect, it should be noted that patients were

6 allowed to continue on maintenance COPD medication

7 throughout the trial.

8   With regard to exercise tolerance, while

9 statistically significant improvements in endurance

10 time and inspiratory capacity were seen, due to issues

11 with generalizability, lack of MCIDs and timing, it is

12 unclear if the improvements are clinically significant.

13   With regard to risk, the safety profile is

14 generally typical for a LABA. It should also be noted

15 that the sponsor's proposed dosing is 5 micrograms

16 once- daily, which is a lower of the two doses studied

17 in Phase III. Selection of the lower dose may

18 theoretically reduce LABA-related safety concerns. It

19 should also be noted that a numerical imbalance in the

20 SOC neoplasm benign, malignant and not specified was

21 also observed.

22   You are now asked to consider the evidence

1 for efficacy and safety together. In closing, as you

2 hear the charge to the committee, which will be

3 delivered by Dr. Michele later this afternoon, and as

4 you discuss the questions posed to you, we hope that

5 you keep in mind this slide. We look forward in

6 particular to your input regarding interpretation of

7 the exercise tolerance data. This concludes the FDA

8 presentations. Thank you for your time. Clarifying

9 Questions to the Presenters

10   DR. JACOBY: Thank you. We'll have questions

11 now. Actually I'd like to ask a question before you --

12 may I ask you? Specifically with your questions about

13 the exercise tolerance claim, and this is going to be

14 an important discussion here, I just want to be clear

15 on what you mean by the lack of generalizability.

16   I mean you're talking about patients that

17 can't exercise for another reason. And the claim is

18 not going to be that this medication is going to cure

19 their arthritis. But what exactly is your objection to

20 the way that these studies were done?

21   DR. LIM: I think our objection is just that

22 -- we just wanted the panel to be aware that there were

1 patients who had COPD who would not be included, who

2 were not included in those trials. And so claims

3 related to that, we wouldn't know if that would include

4 those patients basically.

5   DR. JACOBY: Okay. Thank you. Dr. Thadani?

6   DR. MICHELE: Excuse me.

7   DR. THADANI: I've got a special question on

8 exercise too, so before you leave, and another general

9 question. Now when you analyze the exercise data, you

10 know patients are exercising different workloads

11 because you're selecting 75 percent of the peak

12 exercise. So somebody is able to walk 20 watts,

13 somebody's going to walk 60 watts.

14   So how do you statistically analyze the data

15 given the different -- because when we do an exercise

16 in angina patients, we have either a Bruce or modified

17 Bruce, we've got the same protocol for each patient.

18 So here you have to tabulate why patient X is going to

19 be doing 24 walks, my next patient is 50.

20   I've done that in the past when I was in

21 England for the modified protocol, and you had to

22 really remember it, you have to jot it, patient comes

1 six months later you have to remember you start at the

2 same workload.

3   So there are some human errors there. So

4 should you be doing a non-parametric test because given

5 that like Wilcoxon or do you just do the standard

6 testing? I realize a crossover study, so what's your

7 take on that?

8   DR. ABUGOV: This was tested and the original

9 confidence intervals were given in percent increase

10 compared to placebo.

11   DR. THADANI: I realize that.

12   DR. ABUGOV: And I back transformed those

13 numbers for that slide so that you could see the

14 absolute differences.

15   DR. THADANI: So can you show us the

16 individual data? Because somebody who is at 20 watts,

17 gets symptomatic. His delta generally will be much

18 greater than somebody walks greater.

19   DR. ABUGOV: Yes.

20   DR. THADANI: So how do you -- because is

21 there a statistical issue when you group data with the

22 different workloads? I realize a crossover, don't take

1 me wrong. The delta is good for each patient so is

2 there a statistical nightmare that you can't really

3 generalize data doing this way?

4   DR. ABUGOV: Well I don't think so. You're

5 referring to the possibility of doing sub-analyses.

6 Pardon my voice. You're referring to the possibility

7 of doing sub-analyses on different groups. I didn't do

8 those analyses. So I'm not aware that, of whether

9 those differences exist.

10   DR. MICHELE: The other thing that I'll just

11 point out with regards to that is that we are looking

12 at a fairly wide range of patients here in terms of

13 their FEV1s at baseline. And so I think that this

14 approach is one way to kind of normalize for that.

15   DR. THADANI: Also I think in Europe a lot of

16 people do bicycle exercise. We don't do that much

17 here. In the U.S. we do treadmill more, at least in

18 angina studies. So that's another issue. And there

19 was no -- it was on monotherapy rather than background

20 therapy, so there are several issues with that.

21   Now the general question to the FDA is this.

22 I know acute bronchospasm in asthma is awful, patient

1 has an impending doom of death. He breaths an inhaler,

2 he feels a lot better so dyspnea index gets better.

3 Here we are talking about a COPD. And you're going to

4 give a treatment which is lifelong. And you're

5 improving FEV1 by you know 40, 60 milliliters at

6 trough, which is significant, so it's a bronchodilator.

7 And yet none of the important parameters, either the

8 dyspnea index or other subjective matters, or even in

9 the COPD hospitalizations or death is not different.

10   So why on earth -- if I was a patient, I'll

11 take this medication, pay a lot of money, and there is

12 no final outcome differences, although you can show

13 objectively that FEV1 is better, but it's not

14 translating into any hard outcomes. As a cardiologist,

15 you know we look at hard outcomes. I realize you're

16 pulmonologists, you do different trials, but just

17 curious.

18   DR. MICHELE: Right. So perhaps I can just

19 give a little bit of background on how we look at COPD,

20 and how we look at products for approval. So first

21 off, I'm glad you brought up TDI because I wanted to go

22 back and circle to Dr. Calhoun's comment about that in

1 the previous presentation.

2   So the transitional dyspnea index, as Dr.

3 Calhoun was alluding to, has a number of issues, and

4 this has to do with just the methodology of the test,

5 how the test was designed. It was discussed at length

6 in a Pulmonary Allergy Drug Advisory Board in 2001.

7 Because of these issues, FDA does not recognize this as

8 a test that's appropriate for approving drugs. And so

9 this test is usually included in global programs, such

10 as this, for European approvals. We look at it. It's

11 there, but we don't make very much of it.

12   With regards to bronchodilator efficacy, the

13 most objective measurement of that is FEV1. We

14 recognize that this is a surrogate endpoint, but it's

15 been very well validated over the years, and it is the

16 primary efficacy endpoint for bronchodilation. We do

17 give a separate claim for products that have been shown

18 to improve the COPD exacerbation and prevent

19 exacerbations. That's a separate indication, and not

20 all COPD products have that.

21   That comes up, importantly, in the design of

22 COPD trials because now that we do have three products

1 on the market for prevention of COPD trials, we can no

2 longer do very long-term, one, two, three, four year

3 trials and have patients on strictly placebo. And I

4 think that this is one of the first programs that has

5 really addressed this by having patients on usual care

6 background therapy.

7   So really to dissect out the issues, the

8 exacerbations are totally separate from bronchodilator

9 efficacy, that's symptom relief. And exercise we

10 recognize is another measurement of bronchodilator

11 efficacy. It would not be a separate indication.

12   With regards to labeling, that came up

13 several times in the first presentation. And we don't

14 really need to get into the details of the label here.

15 That's something that's worked out between FDA and the

16 sponsor. So we just noted that what the primary

17 indication is so that you know when you get to the

18 voting questions what you're actually voting on.

19   One other point that I'll bring up that was

20 mentioned in the first presentations, as far as the

21 questions go. There were a lot of questions about

22 manufacturing issues. And the committee is entirely

192

1 correct that manufacturing is an important issue for

2 drug approval.

3   However, it's not one that we discuss in an

4 open public forum, such as this committee, because

5 there are a number of things related to manufacturing

6 that are company proprietary. Rest assured that it

7 reviewed in great detail and the sponsor has all sorts

8 of interactions with the chemistry, manufacturing and

9 controls reviewers related to that. So I'll just

10 mention that and kind of take it off the table for

11 discussion.

12   DR. THADANI: Did you give any data -- I did

13 not see any data on symptom relief. All I saw was FEV1

14 at trough. There's a dichotomy of some of the

15 endpoints of questionnaires or dyspnea index, but is

16 there any other data on symptom relief? And I'm not

17 talking about acute here.

18   It's a chronic disease with a FEV1

19 improvement surrogate endpoint like silent ischemia in

20 patient with CAD would never approve -- I've never seen

21 a drug approved for silent ischemia yet. So is there

22 any symptom relief in the database that you could share

1 with us or you?

2   DR. MICHELE: The sponsor did measure rescue

3 medication use, and there were improvements in rescue

4 medication use. That's very typical for a program such

5 as this. But we do not have any specific measures of

6 dyspnea. There are no PROs that have been validated

7 for measurement of dyspnea.

8   DR. JACOBY: Dr. Calhoun?

9   DR. CALHOUN: I just have a quick question

10 for Dr. Abugov, and I'd like you please to clarify the

11 agency's position, and this is regarding the 24-hour

12 data. You criticized the gap from hours 14 to 23 in

13 the dataset and said that that would -- made it

14 impossible to tell the effect on the diurnal variation

15 of lung function.

16   But in sitting here and thinking about that

17 criticism, I find it a little bit odd because the

18 alternative to wake people up every hour and measure

19 their lung function would also have interfered with

20 their diurnal variation. So what's the agency's

21 position on this?

22   DR. MICHELE: So just to comment on that.

1 You're absolutely correct, there is no great answer to

2 this. If you wake people up in the middle of the

3 night, are the FEV1s that you're getting optimal?

4 Probably not. But on the other hand, we have seen

5 programs that have measured this in small subsets of

6 patients and it does give us a better picture in terms

7 of the FEV1 curve.

8   And I think that's all he was pointing out,

9 was just that there is a gap there and just so that you

10 can be aware of it and take it into account as you're

11 thinking about things. It in no way negates the

12 results that were obtained for the trough FEV1.

13   DR. CALHOUN: Okay, that was really my

14 question. Were you negating or discounting those data

15 on the basis of that gap?

16   DR. JACOBY: Dr. Carvalho?

17   DR. CARVALHO: Thank you. I have two quick

18 questions. First in Studies 37 and 38, I wonder what

19 the agency thought of the Borg scale as being used in

20 exercise, because there appear to be no difference in

21 respiratory discomfort using the Borg scale between

22 studies.

 1   DR. MICHELE: Good question. We have not

 2 used this scale in any drug approval programs. And I

 3 don't know what it means.

 4   DR. CARVALHO: And my second question is,

 5 since we're looking at FEV1 for all of the Phase III

 6 studies, in which we're looking at COPD patients, I'm

 7 wondering what the agency thought of the exclusion

 8 criteria of the asthmatics. It appeared that asthma

 9 had to be excluded based on either source documentation

10 or just kind of clinical questioning.

11   DR. MICHELE: That's very typical for COPD

12 programs and we think it's appropriate.

13   DR. JACOBY: Dr. Blake?

14   DR. BLAKE: My question has to do with the

15 long- term spirometry trials and it's a statistics

16 question. And I may not understand this very well, but

17 when you were describing the change that the sponsor

18 made in their statistical analysis, after the studies I

19 think were completed, what's the difference, if I

20 understood it correctly, when you described the

21 treatment and the interaction with, the term for the

22 interaction with tiotropium versus doing a stratified

1 analysis by tiotropium?

2   So I'm not sure that I understand the

3 statistics right, but from what I understood, initially

4 it was planned to include it as an interaction term and

5 then subsequently it was stratified?

6   DR. ABUGOV: The later analyses

7 stratified by tiotropium were just performed to examine

8 the sponsor's rationale that tiotropium reduces the

9 effect of olodaterol. Now as far as use of the

10 interaction term versus not, when there's an

11 interaction term, it gives patients who are taking

12 tiotropium 50 percent weight in the mean. However, in

13 the actual sample population in the trial, there were

14 only 25 percent of the patients taking tiotropium.

15   So I believe that the applicant's argument

16 was simply that well look, tiotropium has a smaller --

17 olodaterol has a smaller effect on these patients

18 taking tiotropium, they're in a minority, so let's down

19 weight them.

20   However, in the stratified analyses, I show

21 that tiotropium really doesn't have a consistent effect

22 on olodaterol. So, given that we only accept post hoc

1 analyses with an incredibly compelling overriding

2 rationale, we don't feel that a post hoc analysis is

3 appropriate.

4   DR. BLAKE: So what would have been the right

5 way to do it preplan?

6   DR. ABUGOV: To stay with the preplanned

7 analysis, which is what I presented.

8   DR. BLAKE: So but I mean even if they were

9 doing it preplanned, would it have been better to have

10 preplanned a stratified analysis or is it better always

11 to include it as an interaction term?

12   DR. ABUGOV: Well, traditionally the way it's

13 done is that you include an interaction term. And if

14 it's significant, then you need to provide a stratified

15 analysis. In this case, those olodaterol by tiotropium

16 interaction terms were not statistically significant.

17   DR. BLAKE: Okay.

18   DR. JACOBY: Dr. Herring? I'm sorry.

19   DR. BLAKE: May I ask one other different?

20   DR. JACOBY: Yes.

21   DR. BLAKE: This has to do with the exercise

22 test, and this is a -- because I don't know a lot about

1 it in COPD. When the inspiratory time increases, does

2 that parallel endurance time? I mean do they go hand-

3 in- hand?

4   DR. MICHELE: So usually an increase in

5 inspiratory time reflects an increase in dynamic

6 hyperinflation. And so when you're breathing at very

7 high lung volumes, that's incredibly uncomfortable and

8 creates a sensation of dyspnea. So that may directly

9 impact endurance time, if you're very dyspneic.

10   DR. JACOBY: Dr. Herring?

11   DR. HERRING: I just had a follow-up to Dr.

12 Blake's first question. I didn't see anywhere an

13 analysis that had used their prespecified analysis plan

14 of the sponsor for this interaction term, but that had

15 used weighting on the contrast to take into account the

16 fact that only 25 percent of the patients got

17 tiotropium. Since the covariance matrix would be

18 different, I wondered if the FDA had carried out the

19 analysis and whether it matched the significant or non-

20 significant result.

21   DR. ABUGOV: The covariance, you mean?

22   DR. HERRING: Well, in construction of the

1 contrast with the interaction term, if weights -- if

2 you considered using weights to try to just for the

3 imbalance in tiotropium as opposed to eliminating those

4 terms as the sponsor did.

5   DR. ABUGOV: That was certainly a possible

6 approach. I did not look at that.

7   DR. JACOBY: Dr. Greenberger?

8   DR. GREENBERGER: Thank you. I have a couple

9 questions. The first is Dr. Michele or Dr. Lim, you

10 present the sites of the research. Are there

11 regulatory decisions or implications from the quality

12 or the differential benefit from the site of the

13 research since in this report it appears very little is

14 done in the

15 U.S.?

16   DR. MICHELE: There was actually a fair

17 proportion that was done in the U.S. We accept data

18 from all over the world; we just expect it all to have

19 very high quality. We do look at interaction terms,

20 and I believe Dr. Abugov ran that analysis for U.S.

21 versus non- U.S. and it did not show a difference.

22   DR. GREENBERGER: If I could say, I can't,

1 from the slides I can't tell what your ends are for

2 any, where any of the studies were done. I can just

3 see sites or continents.

4   DR. MICHELE: Right. It was roughly 50

5 percent, was that right, of the Trials 11 and 12 were

6 conducted in the U.S.

7   DR. GREENBERGER: Okay. And the other

8 question is, statistically is there an analysis that

9 includes how -- whether the changes that are found are

10 generated by certain few number of sites or is it more

11 across the board? In other words, how consistent is

12 the treatment effect?

13   DR. MICHELE: So we do run that analysis, and

14 we specifically run that analysis to see if there are

15 specific sites that should be audited. But we did not

16 find any particular sites that were driving the

17 analysis.

18   DR. JACOBY: Dr. Thadani?

19   DR. THADANI: In the FDA documents which were

20 sent on those disks, you talk about differential

21 response in asthmatic patients compared to COPD in the

22 sense that hypokalemia was more common in asthmatic

1 patients and also QTc, using Fridericia's equation, was

2 prolonged and that's why you did not see any noise of

3 sudden death I realize in the COPD. What's the reason

4 for the differences? Is it because of the rescue

5 inhalers they use more often in asthmatics or what?

6   DR. MICHELE: Yeah, one thing with regards to

7 the hyper --

8   DR. THADANI: Hypokalemia.

9   DR. MICHELE: Yes, excuse me, hypokalemia.

10 So that was looked at specifically by the sponsor in

11 that particular trial, and they're to be commended for

12 looking at that. You can't find what you're not

13 looking for. So I think that that is really the reason

14 behind why it showed up in that trial and perhaps not

15 in the other ones. But it just goes to show that

16 bronchodilators and beta agonists cause hypokalemia.

17 We all know that.

18   DR. THADANI: So other question is QTc, I

19 think there were 14 patients, can't remember, overall

20 who had a prolonged QTc above delta change more than 30

21 milliseconds. I realize up to 5, 10 we don't care, and

22 if this is true in this subgroup of patients, what

1 happens to my cardiac patients who are some drugs which

2 prolong QT? Do they worry about drug interactions in

3 those people?

4   DR. MICHELE: Yes, so the sponsor did conduct

5 a thorough QT study. It did not show any evidence of

6 QT prolongation at the doses that would be used

7 clinically. So I think that we're probably okay with

8 that regards. All LABA labels do have specific QT

9 language in them.

10   DR. THADANI: And my last question is, when

11 you look at the diurnal rhythm, it seems like peak

12 trough ratio is quite high because you know peak effect

13 is more declined over 12 (ph) hours. And then if you

14 give formoterol there's a bump. Are you better taking

15 a twice-a-day or once-a-day drug in case of nocturnal

16 --

17   DR. MICHELE: Formoterol is a twice-daily

18 drug.

19   DR. THADANI: Yeah. So is there any data on

20 nocturnal dyspnea, specifically in their diaries, how

21 often patients woke up at night in this program to see

22 they didn't have some bronchospasm more at night than

1 during --

2   DR. MICHELE: I don't believe that was

3 measured in these trials.

4   DR. JACOBY: Dr. Calhoun?

5   DR. CALHOUN: Just another statistical

6 question. Was the agency able to see whether there was

7 an interaction between the use of inhaled steroids and

8 the persistence of bronchodilator effect from

9 olodaterol? And understand that that question is

10 confounded by severity, very badly probably because

11 moderate isn't going to be on very much inhaled steroid

12 and severe, more, and et cetera. So is there any way

13 of sorting that out or were you able to take a look at

14 that?

15   DR. ABUGOV: I didn't look at that for the

16 reason you just mentioned.

17   DR. JACOBY: Okay. We're about to break for

18 lunch. Two things before we go. Thing number one is

19 that you should be okay leaving your laptops here, but

20 take any personal items that you want during lunch.

21 Number two, no talking about all of this among

22 yourselves or with anyone else during lunch. We'll be

1 back at 1:00. (A lunch recess was taken.) Open Public

2 Hearing

3   DR. JACOBY: Okay, let's start. We're going

4 to have the open public hearing now. Both the Food and

5 Drug Administration and the public believe in a

6 transparent process for information gathering and

7 decision making. To ensure such transparency at open

8 public hearing sessions of the advisory committee

9 meetings, FDA believes it is important to understand

10 the context of an individual's presentation.

11   For this reason, FDA encourages you, the open

12 public hearing speaker, at the beginning of your

13 written or oral statement, to advise the committee of

14 any financial relationships that you may have with the

15 sponsor, its product and, if known, it's direct

16 competitors.

17   For example, this financial information may

18 include the sponsor's payment of your travel lodging or

19 other expenses in connection with your attendance at

20 this meeting. Likewise FDA encourages you, at the

21 beginning of your statement, to advise the committee if

22 you do not have any such financial relationships.

1   If you choose not to address this issue of

2   financial relationships at the beginning of your

3   statement, it will not preclude you from speaking.

4   The FDA and this committee place great

5   importance in the open public hearing process. The

6   insights and comments provided can help the agency and

7   this committee in their consideration of the issues

8   before them. That said, in many instances and for many

9   topics, there will be a variety of opinions.

10   One of our goals today is for this open

11   public hearing to be conducted in a fair and open way

12   where every participant is listened to carefully and

13   treated with dignity, courtesy and respect. Therefore,

14   please speak only when recognized by the chair. Thank

15   you for your cooperation. Okay, speaker one. We have

16   a speaker? There we go.

17   DR. ROZENBAUM: Good afternoon. My name is

18   Wlodzimierz Vlady Rozenbaum. I have very severe

19   chronic obstructive pulmonary disease and I'm the

20   founder administrator of a major COPD patient support

21   and advocacy group, COPD Alert, which by means of

22   internet networking reaches many thousands of patients

 1 in this country.

 2   Thank you for allowing me to present our

 3 membership's perspective on the drug under

 4 consideration so that the committee will see the

 5 rationale for recommending its approval. I have no

 6 financial interest with any companies and that's as

 7 much as I can tell.

 8   Please consider the following points. COPD

 9 is a chronic, progressive, debilitating disease for

10 which there's no cure. COPD is the only major chronic

11 disease exhibiting increasing mortality rate. In fact,

12 at the end of 2010, the Centers for Disease Control and

13 Prevention declared COPD the third leading cause of

14 death, 12 years ahead of predictions. COPD is also the

15 second leading cause of disability in our country.

16   The prevalence of COPD is growing

17 dramatically. Sixty million already diagnosed, with

18 additional 14 million who do not know that they have

19 it. And the economic burden is staggering as well,

20 nearly $50 billion annually.

21   COPD is primarily comprised of emphysema and

22 chronic bronchitis, both of which may coexist. The

1 disease causes progressive breathlessness, its course

2 is often unpredictable, and can progress rapidly. A

3 great number of patients with COPD have other

4 associated illnesses such as cardiovascular, diabetes,

5 atherosclerosis, depression, which contribute to the

6 overall severity of the disease.

7   There is a great need for innovative

8 therapies in order to make the treatment of COPD more

9 effective. With regard to drugs, it means that we need

10 more medicines specifically targeting emphysema and

11 chronic bronchitis. We have very few of these and we

12 still rely heavily on those developed for asthmatics.

13   It has been established that various

14 subgroups of patients respond differently to

15 medications. For example, there are those of us who

16 experience elevated blood pressure when taking

17 salmeterol, not helpful if we are being treated for

18 hypertension at the same time, while anticholinergics

19 contain warnings for persons with

20 BPH.

21   The mode of delivery also presents challenges

22 to patients. There is an urgent need to develop more

1 medicines which can allow for more effective

2 therapeutic strategies in COPD treatment. It is

3 encouraging to hear that olodaterol helps to improve

4 exercise endurance, that it is beneficial to patients

5 in all stages of COPD, and that it does not pose major

6 safety concerns. We hope that the once-daily

7 olodaterol will effectively complement once-daily

8 tiotropium. Thank you very much for your attention.

9   DR. JACOBY: Thank you, Dr. Rozenbaum. We

10 appreciate your perspective on this. The open public

11 hearing portion of this meeting is now concluded and we

12 will no longer take comments from the audience. The

13 committee will now turn its attention to address the

14 task at hand, the careful consideration of the data

15 before the committee, as well as the public comments.

16   We'll now begin the panel discussion portion

17 of the meeting. Before we get to that, there was a

18 question that Mr. Mullins had about comorbidities and

19 obesity that I believe the sponsor has a response to

20 now.

21   DR. DISSE: I extracted this information

22 requested from our study reports. And the question

1 was, the comorbidities in the exercise tolerance

2 studies, and it's displayed on the slide here. And

3 this is not really different from the other large

4 studies we conducted.

5   As you see, quite a variety of typical

6 comorbidities in the cardiac metabolic field, also

7 osteoarthritis. So I think all that was not a limit

8 for patients to participate in the exercise part.

9   Another question was whether we included

10 patients with obesity, and this was checked. So we

11 used here in the evaluation just performed a BMI higher

12 than 28 kilograms per square meter. And as you can

13 see, more than one-third of the patients were obese,

14 meeting this definition. That is similar to the large

15 trials we performed. Thank you.

16   DR. JACOBY: Great. Thank you very much.

17 We'll now begin the panel discussion portion of the

18 meeting. Although this portion is open to public

19 observers, public attendees may not participate, except

20 at the specific request of the panel. We'll now have

21 the charge to the committee presented by Dr. Theresa

22 Michele. Charge to the Committee

1   DR. MICHELE: So thank you, Dr. Jacoby. Over

2 the next few minutes I will focus on the questions you

3 were asked to consider and try to provide some guidance

4 on the context in which they were written.

5   Once again, we come back to the topics for

6 discussion. For efficacy data, the voting questions,

7 which are fairly standard, will focus on the

8 indication, which is as a bronchodilator in COPD.

9   In addition to the standard efficacy

10 questions, we are asking you to focus your discussion

11 on interpretation and design of the exercise trials,

12 since this represents a new claim for COPD, without

13 regulatory precedent.   There are a number of

14 scientific questions surrounding this claim and what to

15 do with the data. Finally, we ask the standard safety

16 questions.

17   Before we get to the questions, I want to

18 remind you of the laws governing FDA decisions of

19 approval or non-approval which are relevant to how we

20 ask you to consider the questions.

21   The Code of Federal Regulations, or CFR,

22 states that FDA will approve an application after it

1 determines that the drug meets the statutory standards

2 for safety and effectiveness, manufacturing and

3 controls, and labeling.

4   Note that we are not discussing manufacturing

5 and controls, which is product quality, or most of the

6 labeling at this meeting, both of which may affect

7 ultimate approval decisions. We are discussing only

8 safety and efficacy.

9   The regulation also mentions that there are

10 many kind of drugs that are subject to the statutory

11 standards and the wide range of uses for these drugs

12 demand flexibility in applying these standards, thus

13 FDA is required to exercise scientific judgment. The

14 aim of this meeting is to get your views and your

15 scientific judgment on the safety and effectiveness of

16 olodaterol, and this will help guide our regulatory

17 decision making.

18   Let me now discuss the standards of safety

19 and efficacy. Efficacy standards are shown on this

20 slide. The language is from a CFR section on a refusal

21 to approve an application. One clause to note related

22 to this meeting is substantial evidence.

 1   This means that efficacy must be certain and

 2 without any doubt. Vote yes or no for the efficacy

 3 question based on your conclusion as to whether the

 4 labeling claim that olodaterol is effective for the

 5 maintenance bronchodilator treatment of airflow

 6 obstruction in patients with COPD is supported or not

 7 supported by well-controlled clinical trials.

 8   The standards for safety are shown on this

 9 slide. The language is from a CFR section on refusal

10 to approve an application. The regulatory language in

11 these three paragraphs boils down to four safety

12 reasons for non-approval. First, the submission does

13 not have adequate tests to assess safety. Second, the

14 product is unsafe. Third, also in paragraph B3, the

15 submitted results do not show that the product is safe.

16 Or fourth, there is insufficient information in the

17 submission to determine whether or not the product is

18 safe. Note also that these safety standards are

19 relative to the labeled use of the product.

20   This brings us to the questions. So the

21 first question is a discussion of efficacy. We ask you

22 to consider the efficacy in light of the setting in

1 which the trials were conducted, namely with all

2 patients receiving standard of care background therapy.

3   This differed significantly from previous

4 COPD programs that have been brought to this committee.

5 It reflects the changing landscape for COPD therapy,

6 and the new ethical challenges that designs of long-

7 term clinical trials in COPD must face, given available

8 therapies for the prevention of COPD exacerbation.

9   Next, we ask you to discuss the safety data

10 that have been presented, including the known LABA

11 safety issues relating to respiratory and

12 cardiovascular safety.

13   Our final discussion question, where we would

14 like you to particularly focus, is about the proposed

15 exercise claims for olodaterol. Specifically, we would

16 like you to discuss the design of the trials, including

17 the issues laid out by Dr. Lim related to trial

18 duration and timing of exercise testing.

19   Since this is a new claim for us, if you have

20 suggestions as to the optimal design of clinical trials

21 to show efficacy of a drug on exercise in COPD, we

22 would especially like to hear them.

 1   Also, we would like your input on MCID for

 2 exercise endurance and inspiratory capacity in

 3 pharmaceutical trials, as well as the best way to

 4 measure and interpret inspiratory capacity for exercise

 5 claims.

 6   The fourth question is the voting question

 7 for efficacy. Note that you are voting on the proposed

 8 dilating indication and not exercise.

 9   The fifth question is the voting question for

10 safety. We are not asking you if the drug is

11 completely safe. We are asking you if the safety

12 profile in the proposed COPD population, for the

13 proposed use, is adequate for approval.

14   And finally, question six, is where we ask

15 you to bring it all together and balance the scales of

16 safety and efficacy for the proposed bronchodilator

17 indication. Again, you are not voting on the exercise

18 claim. As part of the balancing act, you may wish to

19 consider your responses to questions four and five,

20 since this question is essentially the sum of the two.

21 In other words, in order to vote yes for this question,

22 you must have also voted yes for the previous two

1 questions.

2   I now turn the podium back to Dr. Jacoby to

3 open the discussion questions. Thank you. Questions to

4 the Committee and Committee Discussion

5   DR. JACOBY: Thank you, Dr. Michele. So the

6 first three questions we have are non-voting questions.

7 And the first one is to discuss the bronchodilator

8 efficacy data for olodaterol. Who would like to begin?

9 Yes, Dr. Thadani?

10   DR. THADANI: I think if it came from a non-

11 pulmonologist side this time. I think there's no doubt

12 that the data we have shown, we have been shown that

13 the drug has a modest effect on the FEV1, so as a

14 bronchodilator, in patients who are on maintenance

15 therapy. And looking at the data both at peak and

16 trough, FEV1 increases peak effects being a lot greater

17 than the trough.

18   Saying that, I think I'm satisfied with the

19 bronchodilator effect, but I still think it's a

20 surrogate endpoint, in my judgment because I've not

21 seen anything, but you're giving 48-week treatment, it

22 was assessed at 12 and 24 weeks. It would have been

1 nice to show that the effects are maintained at 48

2 weeks.

3   But more so I think I'm surprised that

4 despite the efficacy, there is no relevance on the hard

5 endpoints, either the hospitalizations for COPD

6 exacerbations or death. I realize the rescue

7 medications were used, but I've not seen any dyspnea

8 score or index benefiting. So if the labeling is just

9 as a bronchodilator of modest severity I have no

10 issues, but I'm concerned that the hard endpoints are

11 not going in the right direction, or any direction. So

12 it could be effective. It might be expensive for the

13 patient. So that's one point.

14   The other point is I think we have to make

15 sure that the labeling doesn't say chronic COPD slash

16 emphysema because otherwise every patient with a gross

17 emphysema who doesn't have a chronic bronchitis

18 component is also going to get it. So I think you have

19 to dissociate that from there. And I'll stop with

20 that.

21   DR. JACOBY: Dr. Calhoun?

22   DR. CALHOUN: So let me disagree just a

1 little bit with my esteemed colleague to my left. For

2 reasons that I believe were articulated by Dr. Rennard,

3 it seems to me that trying to differentiate pure

4 emphysema from pure chronic bronchitis in the clinical

5 scenario is very difficult, and oftentimes cannot be

6 done reliably. We can't make a good estimate of

7 whether a patient's 90 percent bronchitis, 10 percent

8 emphysema, 50/50 or 90/10 the other direction.

9   In that, both patients with emphysema and

10 bronchitis can benefit, arguably differentially, but

11 can benefit from good long-term bronchodilator therapy,

12 I'm not so concerned about the COPD umbrella term in

13 this label.

14   Vis-the matter of whether the harder

15 endpoints, like mortality, hospitalizations and so

16 forth, are effective, I guess I have two thoughts about

17 that. Thought one is that these trials were largely

18 done on the baseline of existing standard therapy, some

19 of which in fact do modify exacerbations,

20 hospitalizations and morbidity.

21   And so it may be that adding olodaterol to a

22 baseline doesn't affect hospitalizations, and that's

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1 really okay, because there is an incremental,

2 statistically significant, in my view, also clinically

3 important bronchodilator effect.

4   So I guess for those reasons I think I'm

5 favorably impressed with the bronchodilator efficacy

6 data, given the context in which the trials were done.

7   DR. JACOBY: Thank you, Dr. Calhoun. Dr.

8 Ameredes?

9   DR. AMEREDES: Yes, thank you. First of all

10 I'd like to applaud the sponsor for pushing the

11 envelope of clinical trials a little bit here, because

12 doing a trial with other drugs on board is a very

13 interesting and important concept. This is the way

14 that physicians see patients.

15   They don't see a clean patient generally with

16 no drugs, no treatment on board. And so when we get

17 into real world types of applications, I have to

18 applaud the sponsor for doing that. It makes it more

19 difficult to tease out the effects, so as a researcher,

20 I would have to say you know I can't assume small

21 variabilities. But at the same time, I just want to

22 commend them for doing that.

1   Secondly, I want to commend them for pushing

2   the envelope on seeking this claim for exercise

3   tolerance. It seems that this is an important facet for

4   people with COPD. It isn't just how well they can

5   breathe; it's what they can do. So if they're limited

6   in terms of exercise, and I'm not talking about

7   exercise per se the way it was tested here, but a

8   flight of stairs, walking uphill, whatever it happens

9   to be, that's how those patients identify their

10 limitations. And I know this because I have relatives

11 that suffer from COPD.

12   So one of the things that I wanted to get

13 clarified under this discussion of bronchodilation is

14 sponsor Slide CE23 on Page 12 of the booklet that was

15 given to us. And as I went through the materials

16 before I got this particular booklet and I was looking

17 at all of the slides that were available, I was

18 impressed with the fact that, for example if we look in

19 the upper panel there, Study 11, day 1, the FEV1 in

20 liters was both starting at the same point, the placebo

21 and the olodaterol points were starting at the same

22 place. And then once the treatment is put in place of

1 course, there's this big rise in FEV1 that we see

2 there.

3   And so then when I looked subsequently at the

4 12-week data, which is shown just below that in Slide

5 CE23 for example, but there are many slides that show

6 this kind of an effect, we're talking about that

7 beginning point. And it almost looks as if olodaterol

8 has lost some of its effectiveness in terms of perhaps

9 area under the curve from the starting point at about

10 1.2 on this particular graph that we're talking about.

11   The placebo is starting at about 1.1 where it

12 was before. But it's interesting to me that after 12

13 weeks there's already shown an effect of being on

14 olodaterol, at least that's the way I'm interpreting

15 this, in those people that are now starting that trial

16 again at 12 weeks.

17   And I didn't really hear any comment about

18 that, even though there's a box around it. And what I

19 mean is, I didn't see a lot of effort devoted to

20 explaining the fact that those folks at 12 weeks are

21 actually starting at a higher FEV1 by about what looks

22 to be about 100 mls. And so I just had a query about

1 that and wanted some clarification from the sponsor

2 perhaps to talk about how they feel about that

3 difference in the data.

4   DR. DISSE: This is the trough effect, which

5 means we see the maintained effect after 24 hours, and

6 that is the start off line. So which means this --

7   DR. AMEREDES: Well it's maintained after 24

8 hours, but what I'm saying is obviously you've brought

9 them back for another test 12 weeks, after being on for

10 12 weeks. So are you saying that the trough is

11 continually prolonged through that period? What is it

12 that you mean by -- I just want to clarify.

13   DR. DISSE: Yeah, the trough is at the end of

14 the dosing interval. So the curve you see is the

15 effect of the drug with the acute administration on the

16 test day. But the patient comes into the clinic and

17 has already taken the day before the dose. So after 24

18 hours he has this level of activity of the drug

19 remaining.

20   DR. AMEREDES: I see. So you're class --

21   DR. DISSE: It's a sustained activity.

22   DR. AMEREDES: You're classifying that as

1 trough effect coming in --

2   DR. DISSE: Yes.

3   DR. AMEREDES: -- to that part of the study.

4 Okay, thank you. Appreciate that.

5   DR. JACOBY: Other comments about

6 bronchodilator efficacy? Dr. Terry?

7   DR. TERRY: I would like to respectfully

8 disagree with Dr. Calhoun in the following sense.

9 Those of us who see, on a daily basis, patients come

10 into a pulmonary clinic, one of the most common

11 complaints is cough and sputum production. So they fit

12 the criteria for a chronic bronchitis, but if you look

13 at everyone who fits that definition, a significant

14 number don't have airways obstruction.

15   My concern is that if we approve this for

16 chronic bronchitis and emphysema, that unless there is

17 a criteria that they have obstructive chronic

18 bronchitis, then a significant number of patients will

19 be getting drug not for airways obstruction. It may be

20 beneficial for mucociliary transport, which is what

21 beta sympathomimetic drugs do, but that's not the

22 question at hand here.

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1   DR. JACOBY: Dr. Calhoun?

2   DR. CALHOUN: I don't disagree with you,

3 Peter. So for me, I'm reading the indication COPD,

4 chronic bronchitis and emphysema. And so that

5 presupposes that there's, for me, that presupposes that

6 there is obstructive lung disease. So I don't disagree

7 with you. If there's simply bronchitis in the absence of

8 obstruction, then I totally agree with you. So we

9 don't really disagree.

10   DR. JACOBY: Dr. Greenberger?

11   DR. GREENBERGER: I also am happy to see that

12 there were physiologic data mentioned, or measured

13 regarding the endurance times, which I think is

14 important to take a look at since we already knew, or

15 we found that the FEV1 responses were significant. So

16 I compliment the explorations in that area.

17   I'm also troubled by secondarily, the point

18 about where it says COPD including, because I think I'm

19 in agreement with Dr. Terry's comments about the

20 verbiage, and I'm not frankly sure where the verbiage

21 came from in the question.

22   DR. JACOBY: Other comments about

1 bronchodilator efficacy? Yes, Mr. Mullins?

2   MR. MULLINS: Yes. My question is still

3 related to pharmacokinetics from the sponsor. I'm

4 trying to understand. Also, I was looking back through

5 the data, and how we left out two major populations,

6 one we already discussed, African-Americans, but are

7 there any data on Hispanics in your study?

8   Because you know there's several concerns as

9 far as comorbidities, as far as obesity in Hispanics,

10 and there the prevalence of emphysema and COPD. So

11 could you help me with that and your analysis? Because

12 I want to be able to make assumptions across the board

13 and avoid generalizations.

14   DR. DISSE: So Bernd Disse, Boehringer

15 Ingelheim. We just had shown the data on obesity, and

16 maybe we can show them please again. So concerning

17 your question you had in the morning, we have

18 investigated the files and the first question you had

19 asked was for comorbidities in our exercise studies,

20 and here is the display of the comorbidities.

21   And so this is perfectly representative of

22 what we have seen in the other large trials, so it's

1 really a huge variety of cardiac, metabolic and joint

2 diseases, and not different from the other trials. So

3 from this point of view the exercise trials are

4 representative.

5   Your next question addressed whether we

6 included patients with obesity, and we checked the

7 files. And --

8   MR. MULLINS: Let me go back to that slide

9 please. So let me be clear, I'd like to go back to

10 that previous slide. So there were only nine percent

11 of the patients that were obese in this study, nine

12 percent?

13   DR. DISSE: I come to this in the next slide.

14 Obesity was checked here on our clinical research form.

15 This means it was a judgment of the investigator,

16 whether he thought the patient --

17   MR. MULLINS: So there was some subjectivity

18 involved in this?

19   DR. DISSE: It is a subjective assessment of

20 the investigator. Therefore, I would like to come back

21 with the next slide, which is extracted from our

22 database in the same studies. And we used a criterion

1 of BMI higher than 28 kilograms per square meter. And

2 following this definition, more than one-third of the

3 patients were obese. This is also representative for

4 the larger trials where a similar figure can be

5 applied. So this is to your question.

6   The next part of your question was the

7 representation of population ethnics. And as already

8 pointed out, I have commented already on African-

9 American participation, which was on the low side but

10 at least gives an anecdotal safety readout. Concerning

11 Hispanics, Hispanics are typically not separated from

12 whites, so they are included. And we believe we have a

13 typical representation of the U.S. American population

14 concerning Hispanics.

15   MR. MULLINS: You classify Hispanics as

16 Caucasian?

17   DR. DISSE: As white. White is now the

18 overriding classification.

19   MR. MULLINS: So you feel the representation

20 of the population is balanced and makes this data

21 statistically sound?

22   DR. DISSE: We think yes.

1   MR. MULLINS: I don't agree with that.

2   DR. JACOBY: Thank you. Other comments on

3 bronchodilator efficacy?

4   DR. BLAKE: I have an issue that hasn't

5 really been discussed much so far, but it's the change

6 in the duration I guess, if you want to look at it that

7 way, but the trough FEV1 over time. And I guess my

8 concern is that you can see quite clearly that the

9 trough FEV1 decreases over the 48-week treatment

10 period.

11   So my question to I think the panel, that I

12 would like education on, is this typical -- I know it's

13 typical for beta agonists. We see a shortening of the

14 treatment interval when it's given regularly. But is

15 it true in -- that's in asthma -- is it true in COPD

16 too? And do you see this with LAMAs as well? I'm just

17 curious as to how this compares with the other drugs

18 used.

19   DR. JACOBY: Dr. Disse, would you like to

20 comment on that?

21   DR. DISSE: If you allow us to comment, so

22 there is a natural rate of decline of FEV1 over time.

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1 That is not a decline of effect, and I would like to

2 invite Dr. Hamilton to review the comparison of the

3 signal size.

4   DR. HAMILTON: Thank you. Yes, I would like

5 to just come back to the core slides, which I think are

6 representing both the AUC and the trough over the 48

7 weeks. And so this first slide was from the core

8 presentation. And to Dr. Disse's point, if we look at

9 both the AUC on the top panels, and the trough on the

10 bottom, what you do see in both the olodaterol and the

11 placebo groups, in both investigational arms, you are

12 seeing a decline in lung function over the 48 weeks,

13 which is representative of the natural course of the

14 disease.

15   So as we know it's progressive disease. And

16 when we consider in the placebo group, the decline over

17 the 48 weeks is, across the studies, of the order of 30

18 to 50 mils, and that is fairly representative of the

19 literature figures on that, there is some variability.

20   So but in these studies, if we take a look at

21 the difference between olodaterol and placebo over the

22 48 weeks, we do not see any evidence that we are losing

1 the effect. So it's more that all patients are losing

2 an effect over time, but the treatment effect is still

3 maintained.

4   And I'd also, just for full disclosure, I

5 think just show the 13 and 14 studies as well, where in

6 14 there was some tendency, maybe on the AUC, for the

7 placebo response not to be quite such a large slope.

8 But overall, when we take a look at the four studies,

9 bearing in mind the natural course of the disease, we

10 do not see any waning of the treatment effect over

11 time.

12   DR. THADANI: Before you leave, could I labor

13 that question? If you go on 13 study, I think it was -

14 - that's your CE26.

15   DR. HAMILTON: So the one we just had up

16 there? Yes, certainly. This one here?

17   DR. THADANI: I don't think you can be that

18 confident. If you look at the trough effects, the peak

19 effects are relatively maintaining. There's a decline,

20 but there's no doubt the trough is, over time it's

21 coming down, and that was my question initially. Why

22 not measure at 48 weeks? It's going to be a lifelong

1 treatment.

2   And you can't say that if you look at the

3 placebo, I think it's just a fluctuation because it

4 declined and then it got better, and then it declined.

5 So I don't think you can sell me that as a pure placebo

6 effect. I think reality is that if you did a

7 statistical analysis at 42 weeks, it won't be

8 significant.

9   DR. HAMILTON: Yes, so we --

10   DR. THADANI: I know it's not the primary

11 endpoint. I realize that. (Inaudible) endpoint.

12   DR. HAMILTON: Yes, and I think there is also

13 one important other consideration. And as we have

14 shown in the data, there is a differential

15 discontinuation rate. So we actually have a higher

16 rate of discontinuations in the placebo.

17   So to a certain extent, we are a little bit

18 more cautious about the precision of the estimates as

19 we go further into the study because we're getting a so

20 called health -- we think we're getting a healthy

21 survivor effect.

22   We haven't looked in an exploratory way, post

1 hoc, at that. There are certain statistical tests,

2 such as pattern mixture modeling, which did support

3 that the effects over 48 weeks are probably somewhat

4 dependent on the differential discontinuation.

5   DR. THADANI: But even on the Study 14,

6 placebo after 18 weeks are relatively flat. So you

7 can't say it decreases over time, and yet your response

8 on trough is decreasing. So I think there's a natural

9 attenuation of effects of beta adrenergic stimulation

10 over time. That might be real. I don't know what will

11 happen at one year. So I buy some of the arguments,

12 but I think it's kind of concerning that with time the

13 efficacy might go down.

14   And I would love to see some harder

15 endpoints, like hospitalization, dyspnea score,

16 anything you could show me that improving the peak and

17 a little bit of trough really makes a difference in

18 patients' lifestyle or any questionnaires you have;

19 that would be very useful information if you have it.

20   DR. HAMILTON: Yeah, sorry. I wonder if this

21 is helpful. So we have measured some of those others

22 and maybe I can go back to some of the symptomatic

1 endpoints that we did look at over 48 weeks. We did

2 look at the transition dyspnea index, which is a

3 measure of dyspnea, albeit the FDA's position on the

4 TDI, as well as the SGRQ over 48 weeks.

5   So if I could just show the TDI. Now, there

6 is the caveat to the TDI, as has been mentioned, that

7 from the placebo response was certainly somewhat

8 unexpected. But if we take a look, we did include an

9 active comparator in these studies, formoterol, and we

10 did see - - now I think one thing to remember here is

11 that the TDI is actually a response from baseline.

12   So you measure the baseline dyspnea index at

13 baseline to get an understanding of the patient's

14 dyspnea rating at baseline. And the TDI is actually

15 asking the patient whether they noticed any improvement

16 compared with baseline. So within the active treatment

17 groups, there is some evidence that the olodaterol is

18 showing the same improvements in the transition dyspnea

19 index compared with formoterol.

20   DR. THADANI: But on the other hand, the

21 placebo is doing wonders.

22   DR. HAMILTON: Yes, absolutely.

1   DR. THADANI: So you could argue -- here

2 you're arguing that lung function is declining over

3 time, and yet the patient is feeling better on placebo

4 after initial improvement on your study drug. So why

5 give the study drug if the placebo does the same thing

6 to the patient?

7   DR. HAMILTON: Yeah, absolutely. And that

8 was certainly an unexpected finding for us with the

9 TDI. And maybe I could just first of all maybe come

10 back to the one where we're showing the 13 and 14. So

11 what's on at the moment is the combined dataset. And

12 this unexpected placebo response was identified in one

13 study and not the other study. So if we could show the

14 13 and 14 separately. Great.

15   So as you can see in this slide on the left

16 hand side is Study 13, and that's where we had this

17 unexpected placebo improvement over time. Whereas

18 Study 14 is, the placebo response is very much more in

19 line with many other studies that have used the TDI.

20   We also did perform a, to try to explore the

21 reasoning for that, we did explore -- to try to get an

22 understanding of whether the differential

1 discontinuation rate was having an impact, and so we

2 did perform an exploratory analysis using pattern

3 mixture modeling, and my statistical colleague will be

4 happy to provide the background to the pattern mixture

5 modeling.

6   It is an analysis that does take into account

7 differential discontinuation. When we did that, we did

8 find that the placebo response was much more as

9 expected. And we did see a maintained improvement in

10 TDI for both olodaterol groups over the course of the

11 48 weeks.

12   DR. JACOBY: Dr. Brantly and then Dr.

13 Herring.

14   DR. BRANTLY: So this is Mark Brantly,

15 University of Florida. Again, this is a question to

16 the sponsor actually. And that is that the rate of

17 decline lung function slides made me think of a couple

18 different issues, also. Were you able to stratify

19 between non- smoking, smoking, or some of the

20 categories of GOLD class? And were there differences?

21   DR. DISSE: It was not stratified for

22 smoking, non-smoking --

1   DR. BRANTLY: Right, right.

2   DR. DISSE: -- but the subgroups were

3   analyzed. And would you like to show the subgroup

4   slides?

5   DR. BRANTLY: So in particular, I'd be

6   interested to know whether the FEV1 0-3 was different

7   for smokers versus ex-smokers.

8   DR. HAMILTON: Yes, so in my core

9   presentation, I've just provided a textual description

10 of the demographic factors, but we do have the slides

11 with the forest plots to actually provide further

12 information. I'm bringing that up now.

13   Now when we're looking at these subgroup

14 analyses, we actually have four sets of analyses. This

15 is a representative example. It's from the combined

16 dataset for 11 and 12, and it's on AUC response. And

17 if I just -- so if you look on the right hand side, you

18 will see smoking status as a demographic factor right

19 at the end, ex-smokers and current smokers. And we did

20 not see any apparent influence of smoking status on

21 AUC. And the same was also true for trough and in the

22 other studies as well. So no obvious influence of

1 smoking status.

2   DR. JACOBY: Dr. Herring?

3   DR. HERRING: I was just going to return to

4 the previous point. If you do have those time profiles

5 by the patterns and the pattern mixture modeling, that

6 could be helpful.

7   DR. DISSE: Can I invite our statistician to

8 explain the model? Dr. Menjoge, please.

9   DR. MENJOGE: So Shailendra Menjoge,

10 statistician at Boehringer Ingelheim. Yeah, the

11 pattern mixture model basically assumes that the

12 patients who complete the study and who do not complete

13 the study have different patterns, and therefore they

14 have different effect size. And the overall effect is

15 produced by weighted mean of the effects from the

16 completers and non- completers.

17   And the one that we used in this project is a

18 model based on a paper by Hogan and others in

19 Statistics in Medicine that was the paper on tutorial

20 in biostatistics. You basically look at the

21 discontinuation patterns and you group the patients

22 accordingly for the regression, random slope intercept

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1 model, and develop weight and mean and compare

2 treatments.

3   DR. HERRING: Do you have the profiles over

4 time within each pattern? And I guess a follow-up

5 question is in the -- it wasn't clear to me, based on

6 the figures, but based on, as it seems that you used a

7 linear trend in time for your testing. Is that true?

8 Or were there indicators for the days? Because the

9 plots make it appear that there are indicator variables

10 for each follow-up time because they're not linear.

11   DR. MENJOGE: Unfortunately, I don't have the

12 profiles to show you on a slide, but we have exactly

13 that. You know we looked at the profiles and what we

14 did find is that patients on placebo, particularly they

15 had really sloping down. And so it was clear that that

16 was really affecting. And we did use the -- actually

17 we did use slope over the log time, because that fitted

18 really better.

19   DR. HERRING: In the pattern mixture model?

20   DR. MENJOGE: Pardon me?

21   DR. HERRING: In the pattern mixture model

22 and in the primary analysis?

1   DR. MENJOGE: I'm sorry.

2   DR. HERRING: Was there a linear term in time

3 or log time in the primary efficacy analysis or was

4 that just based on an indicator variable for the 24-

5 week time point?

6   DR. MENJOGE: The primary analysis did not

7 use any kind of random sloping to set model.

8   DR. HERRING: Okay.

9   DR. JACOBY: Other comments on efficacy?

10   DR. CONNETT: Yes. Dr. Michele, a few

11 minutes ago, included a phrase about prevention of COPD

12 exacerbation. Could you repeat what you said on that?

13   DR. MICHELE: I think in my presentation I

14 was just commenting that we now have three products

15 approved for the prevention of COPD exacerbations. And

16 as such, it's really created a new paradigm, or a

17 paradigm shift for COPD trials long-term, in that there

18 is a concern that if you have patients with severe COPD

19 who are on a placebo for a prolonged period of time,

20 you may be placing those patients at risk of

21 exacerbation if you're taking them off all of their

22 other concomitant medications. And so in these trials

1 that did not occur. All of the patients were allowed to

2 be on their usual care therapy throughout the trials.

3   DR. CONNETT: So, well the exacerbations that

4 were reported were strictly on incidence and moderate

5 exacerbations. I'm wondering if they had information

6 on -- first of all does incidence mean time to the

7 first exacerbation?

8   DR. MICHELE: No, I think we're just looking

9 at number of events. We'll let Dr. Disse comment on

10 that. But I will just point out that these trials were

11 not intended to look at exacerbations. They did

12 include exacerbation endpoints, but the trials weren't

13 designed with that as a primary endpoint.

14   DR. DISSE: Yes, Bernd Disse, Boehringer.

15 The trials were not powered for an endpoint time to

16 first exacerbation. This has to do with the frequency

17 of exacerbations, which is, as was mentioned, reduced

18 on the background of concomitant therapy.

19   As I had shown in the core presentation, in

20 this morning, if you have a look at the slide again.

21 So at the top of the panel, that was a protocol-defined

22 exacerbation endpoint. That is defined on the complex

1 of symptoms plus change in treatment. Change in

2 treatments means prescription of antibiotics or

3 steroids, and time to first exacerbation, and of course

4 there was only a very small numerical reduction.

5   And to capture that endpoint would mean

6 probably double the sample size based on the

7 exacerbation rate in such trials. If you use a softer

8 definition, which is the adverse event reporting, at

9 the bottom of this panel we did see a significant

10 effect, a nominal significant effect. But that's not

11 the official approved definition of an exacerbation.

12   So the bottom line is that under the

13 background therapy, the frequency of exacerbations

14 drops to a significant extent already, and then it's

15 very difficult to show an additional effect, and you

16 need larger, especially powered and set up trials for

17 this purpose.

18   DR. JACOBY: Thank you. Dr. Greenberger?

19   DR. GREENBERGER: On efficacy data, going

20 forward I'd like to have a better handle on non-

21 Caucasian, meaning Hispanic and the heterogeneities

22 within Hispanic, such as Puerto Rican versus non.

1 Because at least analogous to data of bronchodilators

2 that are beta agonists in asthmatics there are

3 differences, as you well know. So I think the agency

4 and the sponsor should plan for that in future studies.

5   DR. JACOBY: Other comments? Okay, then

6 let's go to the second discussion question to discuss

7 the overall safety profile of olodaterol. Who would

8 like to start? Dr. Blake?

9   DR. BLAKE: And this wasn't really a big

10 concern about the neoplasms, but I just wondering if

11 anybody knew if there were any big say retrospective

12 cohort studies with indacaterol that might have looked

13 at this effect to see if there's any kind of class

14 trend for this to occur?

15   DR. JACOBY: Dr. Calhoun, did you have -- no,

16 okay, I'm sorry. I thought you were going to answer

17 that question. So the question was does indacaterol

18 have any similar effects? Sure. Yes, Dr. Disse?

19   DR. DISSE: We are not aware of indacaterol

20 data, but there is a large database out, which

21 certainly we have investigated. And I would like to

22 invite Dr. Suissa, epidemiology expert to comment.

1   DR. SUISSA: Thank you. Samy Suissa,

2 Professor of Epidemiology and Biostatistics, McGill

3 University, Montreal. I have received a fee and my

4 travel expenses are paid by Boehringer Ingelheim to

5 attend this meeting.

6   So in fact this potential signal was

7 investigated in several trials of LABAs, for which we

8 could get some data available. And, I'm sorry I don't

9 know how to -- oh this way. Thank you. So in fact the

10 TORCH trial is the biggest trial that where serious

11 adverse events of neoplasms were reported.

12   And the comparison of the patients were on a

13 LABA, in that case salmeterol to the patients who were

14 not on LABA, either placebo or ICS only, we see that

15 the rate ratio for any neoplasm is really one, with a

16 tight confidence interval.

17   A second trial is the INSPIRE trial that

18 compared salmeterol to tiotropium for a one-year

19 period. And again here the rate ratio of serious

20 adverse events for neoplasms was essentially one, with

21 a larger confidence interval. The POI (ph) trial

22 compared salmeterol again to tiotropium. And in that

1 case again we see no excess risk of neoplasms.

2   In indacaterol trials, and this was one of

3 the questions, were looked as well and when put

4 together we see again no excess incidence of neoplasm

5 SAEs. And when this is all put together, the rate

6 ratio is essentially 1. So in a sense no signal on

7 this basis.

8   DR. JACOBY: Other comments on safety? Dr.

9 Calhoun?

10   DR. CALHOUN: So just to kind of amplify on

11 Dr. Blake's comment, as the safety data were

12 summarized, I believe by Dr. Lim, he said this looks

13 like other beta agonists. And that's kind of the way I

14 view it also, except for the small cell carcinomas in

15 which there were four, I believe.

16   And so even though there isn't evidence of

17 carcinogenicity, it's certainly conceivable to me that

18 in that other beta agonists can act as growth factors,

19 particularly on mesenchymal cells, smooth muscle well-

20 documented, it's conceivable to me that something about

21 this molecule could act as a progression factor.

22   Because it was very odd, maybe it's just bad

1 luck on your part, but it's just very odd that four

2 small cells would crop up in the olodaterol group and

3 none would crop up elsewhere. And so I don't think

4 it's a deal killer with respect to safety, but I think

5 that it does probably warrant some post-marketing

6 surveillance.

7   DR. JACOBY: Dr. Ameredes?

8   DR. AMEREDES: Yeah, I guess I had the same

9 question but wanted to possibly ask, you know I was a

10 little bit shocked frankly to see that, just as Dr.

11 Calhoun mentioned, that out of the six total that were

12 reported for the 10 microgram dose, four of them had

13 small cell. And that was -- and also four of them died

14 out of the six, if I read this graph correctly.

15   So I just had a little bit of a concern that

16 you know, this can happen in research all the time

17 where a group displays odd behavior like this, or

18 unexpected behavior. But with regard to the

19 indacaterol study that was just shown a moment ago,

20 where the number was 1 and it wasn't really different

21 from placebo and it wasn't different from any of the

22 other values that were shown, was that for the

1 totality?

2   I'm not familiar with the indacaterol study.

3 Was that for the totality of all the dosages that were

4 looked at or was there a specific dose, one dose that

5 was looked at? And did any of them stand out like this

6 one might?

7   DR. JACOBY: Dr. Disse, did you want to

8 comment on that?

9   DR. DISSE: May I invite Dr. Suissa again

10 also to review the olodaterol data in context?

11   DR. SUISSA: So the answer is this is a

12 pooling of all the data, all the data for indacaterol

13 at all the doses, to be able to obtain numbers,

14 sufficient numbers for these events.

15   But there was a question about lung cancer,

16 and indeed this is intriguing, so we investigated a

17 couple of different comparisons. Now we're getting --

18 we're now not looking with a telescope, but we're

19 looking with a microscope now, smaller and smaller.

20   So in looking at lung cancers, we compared

21 with observational data. So three very recent

22 observational studies that have looked at the incidence

1 of lung cancer in populations of COPD patients of

2 varying populations at varying stages of their disease.

3   And we see that the incidence rate, these are

4 incidence rates, not rate ratios but incidence rate of

5 lung cancer in these populations vary, and of course

6 vary according to age and vary according to the stage

7 of disease. And these numbers are rather comparable

8 with what we are seeing the olodaterol trial, perhaps a

9 bit lower with placebo, but all rather consistent.

10   And the only one trial where we could

11 actually identify lung cancer as a serious adverse

12 event was the TORCH trial. So in the TORCH trial, the

13 same comparison but in this case the 48-week trials

14 with the TORCH trial, where there were four groups,

15 this was a two-by-two factorial study comparing,

16 involving one of the factors being salmeterol, we see

17 that the incidence of lung cancer, in this case not

18 specifically the small cell, this is lung cancer in

19 general, is very much in line with what is seen here in

20 the trial.

21   But now we're getting in the realm of smaller

22 numbers and of course different populations. These are

1 different trials. One is TORCH, the other one is the

2 olodaterol trials, but still there's no signal that

3 anything is going on with lung cancer. But the

4 microscope was not sharp enough to look at small cells

5 this way, and I think at this point this is the most

6 that we can provide in terms of lung cancer incidence

7 in comparison with other LABAs.

8   DR. JACOBY: Thank you. Dr. Hoidal?

9   DR. HOIDAL: I can't find it. Were the

10 subjects screened for cancer prior to entry into the

11 trial?

12   DR. DISSE: No, they were not screened. We

13 have an exclusion criteria and we are not really sure

14 whether this is kept so well, the exclusion criterion

15 is a cancer diagnosis five years ahead of the trial.

16 So in fact at baseline we had some 9 -- it is a bit

17 variable between groups.

18   Placebo groups had a lower incidence. We

19 have between five and nine percent of prevailing cancer

20 diagnosis in these trials. So patients had any kind of

21 cancer, be it breast cancer in their history, be it

22 prostate cancer.

 1   DR. JACOBY: Dr. Thadani?

 2   DR. THADANI: Obviously, it could be a noise,

 3 you know but you still I have to I think, and if you

 4 approve the drug you have to capture all the data on

 5 the small cell lung cancer.

 6   Now the question to you is if you are putting

 7 the safety and efficacy data together, all I've seen on

 8 the efficacy is that bronchodilator increases FEV1 by

 9 12 to 14 percent. It doesn't improve any hard outcomes

10 like hospitalizations for COPD exacerbation, and maybe

11 something overall in the COPD, it doesn't prevent that.

12   So given that, so I tell the patient, oh

13 yeah, your breathing capacity might increase, I'm not

14 talking about exercise here, and yet you know you're

15 not going necessarily live longer or I've not seen any

16 efficacy data on the dyspnea index or patients being

17 able to walk uphill or quality of life issues.

18   If it is there, that would be useful for me

19 to say okay you're benefiting the patient that way.

20 And then I have to tell him maybe you'll get more

21 nasopharyngitis, incidence is higher, and a bit of

22 arthralgia. So why would I hold the convinced patient

1 to take a drug with some side effects and very little

2 clinical outcome data? Yes, FEV1 yes, but so. Is

3 there any comments from other committee members on

4 that?

5   DR. JACOBY: Other comments about the safety?

6 Yes, Dr. Harkins?

7   DR. HARKINS: It seems to be on par with

8 other LABAs as far as safety, but I just wonder if we

9 look at their use of rescue medications as a surrogate

10 for bronchodilation and symptom relief, it's not super

11 impressive. It's 1 or 1.5 puffs less a day, but if you

12 add that up over the course of time, that might be

13 significant for the patient symptom relief as well as a

14 surrogate for bronchodilation.

15   DR. THADANI: But then if you translate into

16 patient symptom relief, I've not seen any data the

17 patient is feeling (inaudible) dyspneic unless they can

18 show the data.

19   DR. JACOBY: Well let's -- excuse me a

20 second. Let's focus on safety at this point. We've

21 talked about efficacy already. So other issues about

22 the safety profile of this medication? Yes, Dr.

 1 Herring?

 2   DR. HERRING: I'd just like to ask the FDA to

 3 clarify in the voting question, adequate for approval.

 4 Because certainly to show safety, we'd need a sample

 5 size three or four times what these studies have done.

 6   DR. MICHELE: Sure. So it's very difficult

 7 to know exactly what that phrase means, because it's

 8 subject to interpretation, but that's basically where

 9 we're left. I will say that the number of patients in

10 these trials is as great or greater than other products

11 that have come to the market. And so we generally

12 consider the size of the safety database to be

13 appropriate for a LABA in COPD.

14   DR. JACOBY: Other questions with respect to

15 safety? Yes, Dr. Tracy?

16   DR. TRACY: Yeah, thank you. I just, I guess

17 just want to point out again, we talked about the

18 efficacy with the ethnic background. I still kind of

19 wonder if that's not an issue from a safety standpoint.

20 It's just something to think about. You know, if this

21 is a -- if we're considering this a class effect, you

22 know maybe that needs to be considered.

1   DR. DISSE: So we have certainly investigated

2   the Asian subgroup. The Asian subgroup is not

3   different. But maybe in the focus of the interest was

4   the African- American subgroup.

5   DR. TRACY: That's correct.

6   DR. DISSE: Please slide up. So here's the

7   review overall. You may remember that the totality of

8   adverse events in the population overall was about 70

9   percent. This doesn't look different in the African-

10   American subgroup, so it's also about 70 percent

11   adverse events overall. And if you look through the

12   classes of adverse events in the preferred terms

13   reported, so nothing especially pops up.

14   So at least on this small number, we can

15   state that the safety profile in African-Americans is

16   fairly comparable. This is also reflected in the

17   serious adverse events. There are only very few.

18   We have certainly also reviewed the Asian

19   subpopulation. Do you have the -- yeah. So as

20   mentioned, this was a substantial proportion and the

21   totality of adverse events was again in the range of 70

22   percent, here with a slight advantage for olodaterol,

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1 overall somewhat lower, so at 63 to 68 percent.

2   And again, if you look through the different

3 event classifications, for instance in the middle of

4 the table look into respiratory, thoracic and

5 mediastinal adverse events, 45, 34, 48, 40.8. So

6 really I think representative for the population

7 overall.

8   As my conclusion, I would think that the

9 overall representation and analysis of adverse events

10 is also representative for the subgroups.

11   DR. JACOBY: Thank you, Dr. Disse. Other

12 questions with respect to safety? Yes, Mr. Mullins?

13   MR. MULLINS: Yes, I'd like to go back to

14 that previous slide that you mentioned for African-

15 Americans. Could you show me, or stratify the

16 comorbidities of the population that you mentioned in

17 the slide that you had up previously, so I can

18 understand the comorbidities of the population of the

19 African-American population?

20   You mentioned adverse effects but I wanted --

21 you know I don't whether they reflect -- I'm trying to

22 understand -- you're trying to make assumptions about

1 the broad population from limited data.

2   And the problem I have is that I think

3 there's all types of questions from making huge

4 assumptions from small samples. And I don't agree that

5 your data's statistically sound because you're trying

6 to make populations for the entire public.

7   From a public health perspective, I think

8 that certain classes that you excluded, because would

9 feel that this data was reliable, and the data's not

10 reliable. It's really not relevant to them because of

11 what we know about pharmacokinetics.

12   And the fastest growing populations of

13 asthma, just take that particular malady, the fastest

14 growing population, Hispanics are the fastest growing

15 population. The highest prevalence of asthma is in

16 African-Americans.

17   So I'm trying to understand how you can

18 exclude two major populations that represent a large

19 portion of the COPD population and then feel like you

20 can make sound assumptions that are scientifically

21 accurate for the broad population.

22   DR. DISSE: So I mentioned that we did not at

1 all exclude populations. It is just how the

2 recruitment of populations went into the studies. And

3 to be regretted, as I said, the proportion of African-

4 American patients was overall at two percent and about

5 four to five percent in the American part of the

6 studies.

7   Hispanic was not specifically recorded,

8 because included under white. But to assure you of

9 this, there is no evidence for a metabolic difference

10 as concerns metabolism of beta agonists in African-

11 American populations. It was investigated for the

12 Asian population. We can certainly, if you want to see

13 this, analyze the pharmacokinetics, or the influential

14 factors concerning pharmacokinetics.

15   MR. MULLINS: But based on your -- excuse me,

16 based on your trials, there are certain endpoints that

17 I would like to look at that I can't even look at for

18 the most affected populations. These are not just

19 minimally affected populations.

20   These populations reflect the highest

21 prevalence of asthma and COPD. They were excluded from

22 a design standpoint, a design of the trial. I'm

255

1 confused as why we even design a trial that excluded

2 populations with the highest prevalence of asthma,

3 emphysema and COPD. So I wanted you to help me out

4 with that. Why would you even design a trial like that

5 and still consider it statistically sound and relevant?

6   DR. DISSE: I cannot understand why you are

7 saying we excluded by design. I think the study was

8 completely open for all ethnicities. But it seems that

9 sites, where we contracted this trial, do not have

10 access to the -- or do have somewhat limited access to

11 African- Americans. This is not unusual; it is

12 somewhat difficult to recruit African-Americans into

13 these studies.

14   MR. MULLINS: That's not true, sir. African-

15 Americans and Hispanics participate in clinical trials.

16   DR. DISSE: They do.

17   MR. MULLINS: You know that also. They

18 participate in clinical trials, so let's not make

19 generalizations. I think that for us to make

20 statements about public health, not stratify based on

21 certain populations. If we want to make assumptions

22 about public health, then we have to include the entire

 1 public.

 2   So we're making assumptions that, as far as

 3 safety, that I want to be sure. There are certain

 4 endpoints that I would like at, I can't even look at,

 5 for the most affected subpopulations, Hispanics and

 6 limited data on women, women are highly affected, but

 7 particularly African-Americans and Hispanics. I can't

 8 even look at the data because they were not included.

 9 And we know it's possible to include them in clinical

10 trials. It's done quite routinely.

11   DR. JACOBY: Dr. Michele?

12   DR. MICHELE: Just a comment. Again, not to

13 defend the sponsor's studies, but I will say that per

14 FDA guidance, the way to record ethnicity does not

15 separate out Hispanics specifically. It's listed as

16 white, and then under that there's a separate question

17 regarding that, and that's per government guidance. So

18 that's not anything unusual.

19   Also I'll just comment that COPD trials,

20 because we recognize that in asthma certainly African-

21 Americans are more greatly affected, that is not the

22 same in COPD. And we do not generally get a huge

1 representation of African-Americans in COPD trials.

2   So this is actually a relatively large

3 representation compared to other products that are on

4 the market. So just to put that in context. Again,

5 that's not to say that there could not have been a

6 greater representation.

7   MR. MULLINS: Well what I'm trying

8 understand, it seems like the sponsor didn't stratify

9 emphysema patients versus COPD, excuse me, versus

10 asthma patients. So we can't even -- I can't even

11 definitively say how many African-American patients had

12 asthma. So there's limited data.

13

14

15   DR. MICHELE: Asthma patients were

16 specifically excluded from the trials.

17   MR. MULLINS: Okay.

18   DR. MICHELE: Because this is a COPD program.

19   MR. MULLINS: Right. Okay. But emphysema,

20 emphysema there's not definitive data on emphysema.

21   DR. JACOBY: Other questions regarding

22 safety? Okay, then let's move on to the -- oh, I'm

 1 sorry. Dr. Greenberger?

 2   DR. GREENBERGER: I just wanted the sponsor

 3 to verify this. Some 35 to 40 percent of the patients

 4 had, or the subjects had hypertension, and there was no

 5 safety signal. Is that correct?

 6   DR. DISSE: Yes. And the subgroup had no

 7 special safety signal.

 8   DR. JACOBY: Okay. The next question has to

 9 do with the exercise claims for olodaterol, and

10 includes the design of the trials, so the duration,

11 timing and medication and exercise testing, the minimum

12 clinically important difference for exercise endurance,

13 and the increased inspiratory capacity during exercise.

14 Dr. Thadani?

15   DR. THADANI: I think I have several issues

16 with the claim of exercise improvement. One, it was

17 not measured at trough, it's only at peak. It was not

18 on a lot of background therapy which was in the pivotal

19 trials for bronchodilation, so you have no idea what

20 will patients do if they were on therapies, but don't

21 show any improvement even at peak.

22   So I think a lot has to be done if there's --

1 because efficacy is really claimed on trough effects.

2 It's a once-a-day drug so there was no trough effects.

3 So I have some issues.

4   The other thing is I think it's very unusual,

5 I realize people have emphasized that they do a maximum

6 exercise test and then go to 75 percent. That's okay

7 for rehabilitation. It has nothing to do for the

8 clinical efficacy of a study, because for rehab you

9 want to exercise the patient at a sub-threshold of

10 their peak capacity to prevent any adverse event during

11 exercise.

12   And when you said there's improvement of 100

13 seconds or 130 seconds over time, that's a training

14 effect. It has nothing to do with a drug effect. Here

15 you're looking at the drug affect acutely and

16 chronically. So I think in order to show the exercise

17 parameters, you have to design a study, you do the

18 control, take them to their peak performance, then give

19 a drug and show compared to placebo it improves their

20 peak performance, whether it's in time or perceived

21 exertion or whatever you want to look, and I have not

22 seen that.

1   So this 75 percent from the baseline, this is

2 something troubling to me. I'm not used to seeing in

3 cardiology studies, if I've got a patient with angina,

4 I push him to severe angina, that's my endpoint, and I

5 was want to prolong that time to severe angina rather

6 than taking a sub-threshold and improving at 75

7 percent.

8   So I think there is some study design issue.

9 I realize your governing bodies approved this but

10 that's for training, it's not for drug responsiveness.

11 So the data you show, 121, 30 seconds, which has been

12 criticized by the FDA, but that data is on

13 rehabilitation, it has nothing to do with acute

14 studies. So are there any drug studies looking at

15 effects just at 75 percent capacity in any other

16 trials?

17   DR. JACOBY: Dr. Disse?

18   DR. DISSE: So there are very important

19 differences between the use in cardiovascular and

20 pulmonary and can I invite Dr. Casaburi?

21   DR. CASABURI: I'm not sure I'll

22 comprehensively answer all your questions there. There

1 were a lot of issues you brought up. First of all, I

2 actually appreciate the analogy to rehabilitation, one

3 of my favorite therapies.

4   In essence, what we're trying to do is

5 demonstrate -- rehabilitation aims to improve

6 functional ability to do things, to do tasks. And this

7 task of constant work rate testing is really very

8 relevant to functional activities. It's how far you

9 can walk at a pace, how many stairs you can go up.

10   An incremental test, as your cardiology

11 protocols essentially give a task. It's like walking

12 up a hill that continues to get steeper and steeper.

13 It's not an especially relevant thing as to what we do

14 in everyday life. So from that point of view, constant

15 work rate testing actually makes a lot of sense.

16   It is a maximal test. It brings you to your

17 maximum ability to do things. If you measured peak

18 oxygen uptake at the end of a constant work rate that's

19 done at these levels, you actually achieve the same

20 oxygen uptake you do in an incremental test. So it is

21 in the same sense an incremental test.

22   Let me show a slide here that's -- am I

1 bringing this up. This compares some commonly used

2 tests and in the middle is your incremental test on a

3 cycle ergometer versus treadmill that you use routinely

4 in cardiology. And again comparing to six-minute

5 walking test, these might be choices we would have

6 possibly made.

7   Now the guidelines in the pulmonary

8 literature do recommend the endurance test, the

9 constant work rate test, because it simulates the kind

10 of activities you do in everyday life, but also because

11 it's more sensitive to the outcome. You can see here

12 the percent increases.

13   This is a study that was done some 10 or 12

14 years ago by a Japanese group where they gave patients

15 a bronchodilator, oxitropium bromide, before and after,

16 -- the exercise testing before and after, and used

17 three different exercise tests before and after and

18 looked at the responsiveness. Six-minute walk where

19 you ask a patient to walk as far as they can in a given

20 period of time, six minutes specifically, doesn't

21 increase very much.

22   Six-minute walk has problems. It's commonly

1 used for stratification of patients, but as an outcome

2 measure it's very effort and strategy dependent, and

3 therefore isn't dependent on the physiologic ability to

4 exercise as other tests are.

5   The peak work rate and incremental test

6 increases statistically significant, no question about

7 it, but a small fraction because you're just sort of

8 seeing what you push up at that very, very last minute

9 of exercise. Endurance time and a constant work rate

10 test increased, in this case, by 20 percent, a good

11 amount and highly statistically significant.

12   I guess there was one other issue there that

13 was brought up, and I'm going to probably forget it.

14   DR. THADANI: You know the question to you is

15 I have nothing against endurance time because as I said

16 I've used it in angina studies in the '70s. But here

17 you're reducing the workload to 75 percent. And then

18 each patient has a different workload because I realize

19 it's crossover design.

20   DR. CASABURI: Precisely.

21   DR. THADANI: So which is reasonable, but why

22 didn't you show me that the patient who's able to walk

1 a bit more on the treadmill by say 50 seconds is also,

2 also has a less dyspnea index or his functional

3 capacity in daily life (inaudible) better. And also

4 why did you pick a peak not a trough? Because the drug

5 is given once a day, were you worried that there would

6 be no effect on trough?

7   DR. CASABURI: Let me address two issues

8 there. You mentioned before that this was a training

9 effect, that in essence people could go longer because

10 they were trained. Remember these were randomized,

11 randomized order, double-blinded studies, and they may

12 well have done the placebo test first, or done the drug

13 test first. So it's not a training effect.

14   And the other issue was --

15   DR. THADANI: So you got data on Phase 1,

16 Phase II of exercise?

17   DR. CASABURI: Yes. I'm sure the peak and

18 trough effect, excuse me.

19   DR. THADANI: No, I realize, in the patient

20 database because they crossover from drug A to drug B.

21   DR. CASABURI: That's exactly it. Or B

22 versus A, A versus B.

1   DR. THADANI: Have you got a -- Phase I and

2 Phase II, there's no difference?

3   DR. CASABURI: There's no difference,

4 exactly. Thank you for that. And the issue of --

5   DR. THADANI: Why not trough? Because your

6 whole efficacy data is on trough.

7   DR. CASABURI: Yes. No, I'm sorry, the

8 trough versus peak effect. Trough would be an

9 especially pernicious thing to do because these people

10 are taking their bronchodilators at 8:00 in the

11 morning. To observe their trough effect, you'd have to

12 see what kind of exercise they could do at 6:00 in the

13 morning, not exactly when they're up and out.

14   DR. THADANI: But that's the time I want to

15 walk and jog a little bit, you know. I want to see

16 that because you've once-a-day drug. So you can't just

17 have pivotal trials on this and then put a peak

18 efficacy and try to smudge the data and give a labeling

19 that it improves exercise tolerance; every physician is

20 going to use the drug on that basis.

21   DR. JACOBY: Dr. Calhoun?

22   DR. DISSE: Dr. Rennard had a comment to this

1 question.

2   DR. JACOBY: Steve?

3   DR. RENNARD: Thank you. Steve Rennard,

4 University of Nebraska Medical Center, Omaha. I'll

5 just add a couple of comments to the remarks that

6 Professor Casaburi made from a clinical perspective,

7 because I agree with you completely, we'd like to have

8 much more data, obviously.

9   You'd like to know what happens throughout

10 the day, after taking the medicine. You'd like to know

11 what happens over a longer period of taking the

12 medicine than the duration of the therapy in this

13 particular study, and you'd like to know what happens

14 on top of background therapy.

15   But I think we need to put this into

16 perspective of where we are in the COPD world, with

17 respect to addressing what patients actually are able

18 to do. So this I think is the very first time a drug

19 has come up for approval where there's data supporting

20 that it bronchodilates.

21   And then the dots have been connected to show

22 that that bronchodilator effect translates into a

1 reduction in dynamic hyperinflation, with a measurable

2 reduction in inspiratory capacity, and then has the

3 expected effect of prolonging exercise time, admittedly

4 in this laboratory test.

5   This clearly demonstrates that the drug can

6 increase patients' capability to exercise. Now whether

7 that will increase what patients will actually do, and

8 over what duration and whatever, obviously we would

9 like to have much more information.

10   We'd like to have as much information as we

11 possibly could. But this is information that we've

12 never had before, when we deal with patients and when

13 we deal with novel bronchodilators. So that now we can

14 get the discussion of patients' ability to do things

15 into our clinical discussion with patients.

16   One of the issues of course is the drug will

17 improve patients' ability to do things, but whether

18 they actually do, do it at the end of the day is

19 something entirely different, and this is the art of

20 medicine. And so from the clinical perspective, having

21 this information available is extremely important.

22   Now more information is always better. We're

1 information driven people. I think we need to

2 recognize though that this is a novel approach. That's

3 why this discussion today is so very important, is to

4 understand how much information is required to help

5 clinicians inform this discussion with patients. For

6 me, the information, it would be contributory.

7   DR. JACOBY: Thank you, Dr. Rennard. Dr.

8 Calhoun?

9   DR. CALHOUN: Okay, for reasons nicely

10 articulated by Dr. Casaburi, I'm not concerned about

11 the constant work rate test. I think that's a

12 reasonably valid test. I think the question of whether

13 to do this at trough or some other peak, or some other

14 time of day, depends a little bit on how the drug is

15 used. As noted, patients really aren't exercising at

16 6:00 in the morning.

17   It would be informative, I guess, to have

18 some data at 2:00 to 4:00 in the afternoon when they

19 might be maximally active, and so to the extent that

20 one can get some data in that regard during normal work

21 hours, that would be useful.

22   I do have a question for the agency.

1 Presumably the sponsor in approaching the agency about

2 how the exercise trials might be conducted, asked you

3 for some guidance. And so is it fair for us to ask you

4 what guidance you gave them to put these things

5 together?

6   DR. MICHELE: Sure. So we actually didn't

7 give them any guidance, because this was not something

8 that we talked about. So where we have the program

9 here now, and that's as much as we have. I would just

10 make a comment regarding exercise at 6:00 a.m. First

11 off, I happen to like exercise at 6:00 a.m., but I may

12 be one of those strange people.

13   There is nothing in the product guidance that

14 says what time of day you have to take this product.

15 It just says that you have to take it once a day,

16 preferably at the same time of day. So there's nothing

17 to say that we couldn't dose this at 2:00 in the

18 afternoon and then test people at 6:00 in the morning,

19 or 8:00 in the morning, or 10:00 in the morning. So I

20 don't think that that argument quite holds water.

21   DR. JACOBY: Dr. Brantly? I'm sorry.

22   DR. CALHOUN: I was just going to follow up

1 on that, just to say that the use of a bronchodilator

2 outcome that has a consequence on exercise capability

3 is probably of clinical importance, as we saw. The

4 question, the second point there on your slide, the

5 clinically important difference for exercise endurance

6 and inspiratory capacity and all those sorts of things,

7 as you mentioned, Dr. Michele, we'd like to be data

8 driven. We'd like to have evidence to support all of

9 that, but I'm not sure that we're there yet

10 And so perhaps a way forward would be for the FDA to

11 convene a panel of cardiologists and respirologists who

12 deal with this sort of testing and get a consensus

13 statement that could then serve as the basis for some

14 FDA guidance here, because as has been mentioned,

15 exercise capacity is a pretty important thing for

16 patients with COPD.

17   They're limited in what they can do. And in

18 point of fact, a change in the distance from 150 feet

19 to 200 feet that they can walk comfortably may be the

20 difference from getting from my office to their car or

21 not.

22   So having some guidance that could be applied

1 for sponsors who have products that might impact

2 exercise could be helpful, because breaking new ground

3 is always challenging, and without specific guidance,

4 it's going to be hard for us to make progress.

5   DR. JACOBY: Dr. Disse?

6   DR. DISSE: I'd like to invite Dr. Casaburi

7 and then Dr. Hamilton to outline.

8   DR. CASABURI: Addressing specifically the

9 issue of clinically important difference, it has to be

10 acknowledged that we're not all the way there. Getting

11 clinically important differences for anything is tough,

12 for exercise -- I'm sorry, for a laboratory-based thing

13 is even harder. I mean witness the fact that we really

14 have no well-accepted clinically important difference

15 for FEV1. So it's not all together surprising that we

16 don't have one that's in stone for the constant work

17 rate exercise testing.

18   On the other hand, we do have some society

19 guidance. There is a good study, first of all, it was

20 Cazzola and I think that Dr. Hamilton has some data

21 that may be helpful.

22   DR. HAMILTON: Yes, I think really we

1 certainly are very much in alignment with the agency's

2 perspective on the lack of a well-substantiated MID on

3 exercise tolerance (ph). We've had actually, as a

4 company we've had quite some experience over the last

5 10, 15 years of conducting these exercise studies.

6   And with the design of the olodaterol

7 studies, we were informed by our previous studies, most

8 notably two studies that we conducted with tiotropium.

9 And I think that's important in relation to the

10 discussion of MID because what was presented in the

11 briefing document, and what has been discussed today,

12 is an MID which is based on absolute seconds.

13   Having run some tiotropium studies and

14 looking retrospectively back at the data, one thing

15 that we found which informed us about our olodaterol

16 studies was that endurance time is non-normally

17 distributed. Therefore, we were actually the -- these

18 two studies of olodaterol are the first studies to go

19 to what we believe is a more appropriate method of

20 analysis, which is on log transform data.

21   So I think that has to be brought into this

22 (inaudible) of an MID, whether an MID truly should be

1 based on an absolute seconds, when you are considering

2 it in terms of the mean effect versus the MID.

3   However, what we did also consider was, given

4 that as a background, we can -- there's another way of

5 looking at the MID, which is not assuming a

6 distribution, and that's by looking at responders. So

7 defining the MID as a threshold and then taking a look

8 at the treatment group versus placebo and seeing how

9 many patients have a greater than that response.

10   So as Dr. Casaburi said, what we did, just

11 for an exploratory analysis, was to consider the ATS

12 and ERS position paper on clinical outcomes in which

13 they do refer to a proposed, and albeit they also

14 mentioned that there's still a lot of work that needs

15 to be done with the MID, but they proposed a range of

16 46 seconds up to 105 seconds.

17   So we thought that that would be a reasonable

18 place to start and to say let's take that 46 seconds

19 and the 105 seconds as a threshold and then see how

20 many patients, when they were on olodaterol, went

21 beyond that and how many on placebo.

22   And so I've got two slides to show you here.

1 So this is now looking at a responder analysis, taking

2 the 46-second threshold. And the right hand side is

3 more statistical inferences, but I think probably what

4 is probably more meaningful to people is if we look at

5 the column of responders.

6   And as we can see in Study 37, with the 46-

7 second threshold, about 28 percent of patients when on

8 placebo had a greater than 46-second improvement;

9 whereas, with olodaterol it was up at 38 percent. And

10 using the odds ratio this was statistically significant

11 for the 5 micrograms but not for the 10. We also found

12 that relatively similar agreement with Study 38.

13   And just as a second analysis, we also then

14 performed the responder analysis using the higher

15 threshold of 105 seconds. And we found that -- now in

16 this study the percent of placebo patients actually

17 responding was somewhat less.

18   But again, we did see consistent results

19 where we show that the number of patients who crossed

20 that 105 second threshold was also greater for

21 olodaterol compared to placebo.

22   So while there is still a lot of debate about

1 the MID, this is certainly one way of taking current

2 propositions for an MID and rather than assuming -- so

3 not assuming any distribution in the analysis but

4 rather looking at responder, we do show some evidence

5 that patients on olodaterol are performing better than

6 placebo.

7   DR. JACOBY: Thank you. Dr. Brantly?

8   DR. BRANTLY: So again this is, obviously

9 this is one of the most interesting questions of the

10 time and thinking about (inaudible) and I'd like to

11 divide it up into two categories. One is the

12 measurement that we use, choosing an inspiratory

13 capacity, how much validation there is regarding how

14 that truly reflects air trapping, and how any change in

15 inspiratory capacity will decrease air trapping in a

16 lot of ways.

17   And so there's some early talks about how to

18 do this, but I think we're still in the pretty early

19 stage of using this and really saying that if you

20 decrease your inspiratory capacity by X, you will have

21 symptom relief and some types of things from that

22 standpoint. So I think there's a lot of people still

 1 working on those areas.

 2   But the second thing again is the minimally

 3 effective, clinically effective effect. And so when

 4 you think about these things, and I think it was

 5 brought up by an earlier speaker, it's really about

 6 whether it affects somebody's ADL.

 7   If it doesn't affect an ADL, if the time is

 8 45 seconds but that doesn't translate into any ADL a

 9 patient does, it's meaningless, quite frankly, because

10 it doesn't translate into any kind of positive thing.

11 (Inaudible) just measuring a number, you can show a

12 difference from that standpoint.

13   So as we think about this, again looking at

14 45 or 50 seconds or even 100 seconds, does that

15 translate into any modification in ADL that you can

16 think of? And so in framing it, I had a bit of

17 difficulty thinking about how 50 or even 100 seconds

18 would really change something.

19   My patient will be able to take a shower

20 longer. My patient would be able to walk further, would

21 go to the mailbox and such. And I think that's

22 something that requires a little discussion on our

1 part, because we can measure things. The question is

2 in measuring them, does it make any difference?

3   DR. JACOBY: Dr. Blake?

4   DR. BLAKE: This is more just a comment. I

5 mean I liked the strategy for the exercise testing. I

6 thought, having done many exercise challenge tests in

7 asthmatics, I liked this design because I thought it

8 introduced an element of control that we didn't really

9 have like when I did treadmill tests in exercise. So I

10 liked that, and I think that and I think that this is,

11 what BI has done is something that I think we can maybe

12 use as a jumping off point for standardizing these

13 kinds of tests.

14   And I also liked the two-hour, doing it at

15 the two-hour time point because that's when patients

16 are getting up. They're probably maybe even the

17 busiest time of their day if they're trying to get out

18 of the house, get to a doctor's appointment or wherever

19 they're trying to get to.

20   But I would also have liked to of seen

21 something that was later in the day so it might have

22 covered kind of their whole busiest part of their day

 1 from 8:00 in the morning until, you know 5:00 or 6:00

 2 in the afternoon would have been helpful.

 3   I don't necessarily think an end of the

 4 dosing interval test would add a whole lot clinically

 5 when we really want to see how these people improve

 6 their lifestyle during the busiest part of the day.

 7   But I would also echo what Dr. Brantly was

 8 just talking about, is how do you translate these

 9 improvements into clinically important differences that

10 patients are going to be able to assess.

11   DR. JACOBY: Dr. Tracy?

12   DR. TRACY: And just to keep going a little

13 bit more on that, I think sometimes as we look at these

14 seemingly small differences and changes, remember we're

15 talking about populations, but what we really take care

16 of is people, patients.

17   So an individual patient may do really well,

18 and maybe that 100 feet makes a big difference. But if

19 you're looking at an average, maybe some people do

20 great. And it kind of goes back to that responder issue

21 that came up a few minutes earlier; it would be nice to

22 figure out who those responders might be ahead of time.

 1   DR. JACOBY: Dr. Herring and then Dr.

 2   Greenberger.

 3   DR. HERRING: I just have a comment about

 4   design of future trials. I think I would really like

 5   to encourage the sponsor to think about longitudinal

 6   design, you know throughout the day so that if you

 7   could get the patient at two hours post, at four hours

 8   post, some meaningful times, then you could maximize

 9   your power.

10   And certainly, I think the results are very

11   interesting, but if the look at the lung function plots

12   from the 24-hour data, it certainly does seem to be the

13   case that two hours in many ways is optimal. And so to

14   look at some of those later times, I agree not

15   necessarily the trough, but more of a profile within

16   subject if it can be tolerated would be nice.

17   DR. JACOBY: Dr. Greenberger?

18   DR. GREENBERGER: Regarding the studies, I

19   think initially one doesn't know if you can reject the

20   null hypothesis with the new drug in the exercise

21   setting. So I think it makes a lot of sense to study

22   at a peak, or it's not really a peak effect, but we

1 know the long- acting drug starts working in five

2 minutes, so I think the two hours is a good time to see

3 whether you find any effect there at all.

4   And also they did not withhold the other

5 medications such as inhaled steroids and some of the

6 other medicines, although they did modify temporarily

7 the LAMA. And that's different from what happened with

8 indacaterol where those drugs were withheld. So they

9 were exploring this in the setting of more of a real

10 life experience and they found the difference.

11   DR. JACOBY: Dr. Thadani?

12   DR. THADANI: In the protocol you're showing,

13 I'm not criticizing, you're showing a definite two-hour

14 effect on the drug, it improves exercise tolerance in

15 the protocol used. I mean, there's no argument on

16 that. But the differences are patients who are able to

17 go to 20 watts may show more effect than a guy who goes

18 to 60 or 80 watts, he might not be able to do more.

19   So I think when you show the database on the,

20 not only the improvement, I think you should probably

21 show the figure on individual database to see where the

22 starting point on placebo is because there's some 20

1 percent placebo response there, too. So it would be

2 nice to look at each patient, how crisscrossing they're

3 doing.

4   So I think there's nothing wrong with that.

5 There are studies in cardiology; drugs have been

6 approved for an improvement of 25 seconds exercise

7 tolerance, 25 seconds, okay. And the problem is there

8 is a dichotomy of treadmill testing or bicycle testing

9 and the diary because when we give them diary for

10 angina frequency, patients don't exert. So unless you

11 can keep the workload, you know sometimes there's a

12 dichotomy. It would be nice to see the angina

13 frequency goes down and exercise going up.

14   But I think for your dyspnea index, it was

15 really reassuring that everything is going in the right

16 direction and the patient feels less dyspneic, so

17 probably if you have the diary data of quality of life,

18 that really substantiates all the claims would be very

19 useful.

20   DR. JACOBY: Dr. Ameredes?

21   DR. AMEREDES: I guess to build a little bit

22 on Dr. Tracy's comments and also what Dr. Blake said,

1 you know, it got me to thinking when I read about this

2 study, just thinking about the whole psychology of

3 exercise and activity. I mean people tend to do

4 things, or do more of things that they're having

5 success with, and they tend to do less of things that

6 they're not having success with.

7   So if they're having pain, difficulty

8 breathing or whatever it is, they're going to modulate

9 their activity downward because of that. If they're

10 having success with their activity, and we've provided

11 them a window of opportunity to maximize their activity

12 in some ways, whether it be exercise in a test or going

13 up that extra flight of stairs, that seems desirable to

14 me.

15   And so one of the questions I had, maybe Dr.

16 Casaburi can address this, what about the idea of is it

17 possible that utilization of this drug, in combination

18 with rehab, would actually be even more beneficial for

19 patients than the two separately.

20   DR. CASABURI: Well, that's an attractive

21 hypothesis and in fact we conducted a study, published

22 I think six, seven years ago, with a combination of --

1 with looking at tiotropium, sponsored by our friends

2 here at Boehringer Ingelheim, where we did a

3 rehabilitation program and randomized patients in a

4 blinded fashion to receive either tiotropium or

5 placebo, back then against the background of no

6 maintenance bronchodilator therapy, probably wouldn't

7 do that now, and found in fact the presence of a good

8 bronchodilator amplified the effects of rehabilitation.

9   Because presumably they were able to do more

10 work as part of their rehabilitation program, their

11 exercise programs and were able to improve their

12 overall fitness. So the concept is there. The concept

13 is there. If patients do more, they'll get more

14 benefit.

15   There's some doubt as to whether people will

16 change their behaviors because you allow them to do

17 more, but that's not something you would expect a

18 pharmacologic agent to do. But in fact the ability to

19 do more is a good thing to do.

20   DR. JACOBY: Dr. Carvalho?

21   DR. CARVALHO: Thank you. And just as a

22 follow up, it appears that although about 25 percent of

1 patients were on tiotropium during the pivotal trials,

2 if I'm correct LAMAs were not allowed in Study 37 and

3 Study 38. Is that correct? So again, we're looking at

4 exercise function without a LAMA on board. I wonder if

5 the patients would have had better Borg scales, better

6 clinical response, and perhaps better duration of

7 treatment and exercise capacity.

8   DR. DISSE: (Inaudible) patients were

9 switched to ipratropium, and this also makes a

10 difference. So they were on two drug classes. As

11 concerns the totality of results, including the Borg

12 dyspnea scale, Dr. Hamilton.

13   DR. HAMILTON: Yeah, so absolutely, in terms

14 of tiotropium, and again, I think it has been mentioned

15 a few times that this is rather novel. And I

16 particularly like the remark of the intention was to be

17 able to truly show that we have a relationship.

18   So we did want to optimize the trial

19 conditions in order to be able to show that our product

20 did have an effect on exercise tolerance. So that was

21 a very specific reason why we removed tiotropium

22 because we have run a number of studies with tiotropium

1 showing it has benefit on exercise tolerance.

2   But although patients were not required to

3 switch from tiotropium to ipratropium, they were

4 allowed to. So what we actually found during the study

5 was I think it was about half the patients who were on

6 tiotropium coming into the study, when they were

7 withdrawn from tiotropium they went on to ipratropium.

8 So they did have a background therapy of ipratropium

9 and ICS and xanthines, but they were not allowed to be

10 on tiotropium.

11   DR. THADANI: From that question, did the

12 patient on the morning of the exercise take their other

13 drugs or no? You know I know you're doing a peak. So

14 the patient comes to the clinic in the morning, do you

15 withhold other bronchodilators or --

16   DR. HAMILTON: Yeah, we followed the standard

17 process in terms of --

18   DR. THADANI: Is the drug given or held?

19   DR. HAMILTON: We have specific criteria. I

20 think this is the same for most --

21   DR. THADANI: No, is the drug held in the

22 morning of exercise testing or no?

 1   DR. HAMILTON: No, so they -- before

 2 exercise, as we -- we follow the same type of procedure

 3 as we would do with pulmonary function testing, which

 4 is to withdraw the bronchodilators prior to the

 5 exercise.

 6   DR. THADANI: So if it's a short-acting drug,

 7 you can't be sure if you're given that would we see the

 8 same exercise response. Why do we withhold other drugs

 9 on the day of testing? Because patient in routine life

10 is taking every drug, here your investigation drug or

11 placebo, I know you're looking at the drug effects.

12   But why you want to withhold all the therapy

13 in the morning? That means you're trying to maximize

14 your peak effects without any background therapy. I

15 realize it's trough, but some drugs, so you know -- is

16 there any data that if you give other drugs and then

17 you do a two- hour peak, you'll see effect?

18   DR. HAMILTON: Yeah. So if I understand your

19 question correctly, you're wondering if we can show

20 additive effects when adding olodaterol and so on. So

21 certainly these were not designed from an additivity

22 point of view. So when we talk about background

1 therapy, where there's usual care, they're not studied

2 to specifically look at the effects of one drug on top

3 of another.

4   We do have other programs, combination

5 programs, where we are specifically looking at that.

6 We have olodaterol and tiotropium. And in those ones,

7 where you co-administer the two drugs together, then we

8 will be further evaluating the effects of the

9 combination on top of the individual drugs.

10   DR. THADANI: But the usual care is

11 withholding therapy in the morning of the test is?

12   DR. HAMILTON: Yes, absolutely.

13   DR. THADANI: Okay.

14   DR. HAMILTON: Yes, that's correct.

15   DR. JACOBY: Mr. Mullins?

16   MR. MULLINS: And that was similar to my

17 question. I wanted to know, is that timing of the bike

18 testing and understand that, were they going from a

19 point of rest to exercise? Because I think the

20 heterogeneity of what I was referring to earlier, of

21 your population, when you look at the general

22 population, they're working, there's a lot of

1 cumulative effects go into when they exercise, or just

2 how they would make assumptions about the capacity

3 expansion or the additional capabilities they will have

4 with olodaterol. And so I want to make sure that they

5 will make the same assumptions that you're making, or

6 you need to give them prerequisites so they can make

7 accurate assumptions.

8   Because was this drug most effective in the

9 morning, when they were going from a point of rest? Or

10 you know -- that's why I think the time of day is

11 important to me, because there's a working class of

12 people that they will have the question about

13 sustainability. They might exercise at the end of the

14 day from a long work day. Will efficacy be sustained

15 at the end of the day or did we set this up to be a

16 morning peak performance type of issue? That's what

17 I'm trying to understand.

18   DR. DISSE: No, that's a very relevant

19 question. So as is tradition, so to say, in COPD the

20 drug was administered in the morning to cover up for

21 the day activity, and less of a problem during

22 nighttime. To cover up the 24-hour duration, we can

1 only use a surrogate. And I need again Dr. Hamilton to

2 show the data on inspiratory capacity, maybe as the

3 closest link to the exercising endurance capacity.

4   DR. HAMILTON: Yeah, so maybe just to go back

5 to the, I guess the foundational hypothesis on which

6 these studies were founded and that was that the

7 reductions in, or the improvements in, airflow and

8 throughout the program we have assessed improvements as

9 airflow using

10 FEV1.

11   So we felt that we had a very good indication

12 that as a bronchodilator we were improving airflow. So

13 we wanted to understand whether that improvement in

14 airflow would translate into improvements in

15 hyperinflation, so reduced hyperinflation during

16 exercise. And with the theory that, and I think a

17 well- founded theory now, that by reducing the

18 hyperinflation during exercise, that would allow

19 patients to go longer.

20   Now, so specifically with exercise, we only

21 measure the exercise two hours post-dose. But we did

22 look at the other component, which was inspiratory

1 capacity at other times of day. And so we did measure

2 inspiratory capacity pre-dose on after six weeks, and I

3 can show that.

4   So this was all patients had to perform a

5 body plethysmography maneuvers, which is generally

6 primarily used to measure lung volumes and to measure

7 function residual capacity. But in addition, because

8 you do an inspiratory maneuver, we also have

9 information on the inspiratory capacity.

10   This is at rest, so it's not during exercise

11 but it's at rest. And shown on this slide, in both 37

12 and 38, if you look at the, minus 30 so that's 30

13 minutes pre-dose, we were able to show significant

14 improvements in inspiratory capacity. So in other

15 words, at rest they were showing a reduced lung

16 hyperinflation.

17   We would want to be very cautious though

18 about over-interpreting that in terms of has that

19 translation to exercise. So for sure we don't have

20 that on exercise, but at least, if you like, we feel

21 we're moving one step closer to that in terms of being

22 able to now show that the airflow, the improvements in

1 airflow have now translated into a reduced

2 hyperinflation. But I think we would not want to

3 extrapolate that to say that that is confirming

4 exercise. We would have to measure that directly.

5   MR. MULLINS: Right. See that's my question

6 about the data and the bicycle testing. Was the

7 testing conditional based on lifestyle? That's what

8 I'm saying. And understanding when and how you did the

9 testing, and based on different populations, will

10 affect the results. Because certain lifestyles, based

11 on work habits, certainly will affect the assumptions

12 that you can make about efficacy, within this exercise

13 test.

14   DR. HAMILTON: Sure, and I think you make a

15 very relevant point in terms of, if I'm understanding

16 you correctly, it's to what extent can we extrapolate

17 from this data into what the patient is doing? And I

18 certainly think that that is something that would

19 probably be something that the individual physician

20 would have to look at the data, the evidence base

21 that's there.

22   But we do feel by having this in the label,

292

1 that allows them to at least see some data, and then

2 understanding that they would have to then, themselves,

3 make an interpretation of what that data means for

4 their individual patient.

5   DR. DISSE: I would like to propose that Dr.

6 Rennard comments. I think you had anyway a comment to

7 the correlation to activity of daily living.

8   DR. RENNARD: Steve Rennard, University of

9 Nebraska Medical Center, Omaha. Thank you Dr. Disse.

10 As Dr. Brantly correctly pointed out, it's really what

11 people actually do that makes a difference, not so much

12 - - I mean, it does matter what their physiology is.

13 But what matters to them is actually what they are

14 doing in daily life.

15   This is not something that we particularly

16 measure well, certainly not in the COPD area. And I

17 think that it's important to understand how people with

18 COPD, in general, are affected by their disease. The

19 disease develops slowly and rather insidiously,

20 especially at the beginning, and people get short of

21 breath, particularly when they exert.

22   And the way they deal with this is they

 1 become remarkably sedentary. By not exerting,

 2 shortness of breath can be avoided. And in fact people

 3 can become remarkably inactive and not necessarily have

 4 any complaints.

 5   There are some COPD patients, some here, who

 6 remain remarkably active throughout the course of their

 7 disease. But the usual experience is that people with

 8 COPD end up with a remarkably restricted life, or at

 9 least lifestyle, which is a consequence of their

10 disease, but also makes their disease worse. They

11 become physically detrained. The detraining is a

12 consequence of their lack of activity, which in turn

13 depends on their reduced physiology.

14   Well to reverse this process is not a rapid

15 one. Pulmonary rehabilitation remarkably can improve

16 patients' sense of wellbeing, quality of life.

17 Activities of daily living however, probably at least

18 measured by activity monitors, can improve but probably

19 improve much more slowly than many of the other

20 measures.

21   And while the data on activities of daily

22 living are relatively sparse, I think it's not hard to

1 think that habits that have come into a lifestyle

2 that's been affected by a disease as insidious as COPD

3 is, that it make take a long time for those habits to

4 change.

5   So from a clinical perspective, I think it's

6 also important to recognize that people with COPD often

7 have tremendous fear about over-exerting themselves.

8 They don't want to get into circumstances where they

9 feel extremely short of breath.

10   And so that it's important to be able to say

11 to people, yes we can optimize your physiology; this

12 will improve your capability of doing things. And then

13 try to motivate them to change their lifestyle in a way

14 that's meaningful for them.

15   And to be honest, improving your exercise

16 time on a 75 percent peak maximal work test by 50

17 seconds or 100 seconds or something like this, is not

18 something that's in and of itself going to be a

19 meaningful effect.

20   It's going to matter whether somebody can

21 walk a distance to be able to go to their

22 granddaughter's ballet recital, and to do that without

1 experiencing uncontrollable dyspnea, or whatever other

2 activity is meaningful for that individual patient.

3   What having this kind of information means to

4 the clinician is that you can now begin to connect the

5 links. A bronchodilator will improve airflow; that's

6 the defining feature for people with obstructive lung

7 disease, what we're talking about today. That's

8 connected to people's ability to exercise, and that

9 then can be connected to what people can do.

10   Now as mentioned many times, we would like to

11 be able to see lots more data to collect lots more

12 dots. But not having that conversation at all, because

13 there's no data, obviously doesn't help anybody go

14 forward. So having these data, I think, can very much

15 help a clinician trying to improve what a patient's

16 doing.

17   MR. MULLINS: But let's just -- and I'm

18 asking very directly, for the working class public that

19 is assessing this new therapy, if they make the

20 assumptions, a lay person, they make the assumption

21 that they will have greater capacity, can they assume

22 if they dose, their dosing is in the morning, when they

1 walk home from the bus and have to take two flights of

2 steps up to their apartment or condo, can they assume

3 that they will have the same outcomes that you assert

4 in the clinical trial?

5   So that's what I'm saying too, will they have

6 greater capacity? Can we make that assumption? Or if

7 they decide to exercise at the end of the day, or the

8 middle of the day, will they be able to see the same

9 outcomes as you saw in the bike testing in the clinical

10 trial?

11   DR. RENNARD: Right. And I'll respond to

12 your question, but your question is completely the

13 appropriate one from a public health perspective. I'll

14 say this, that what the data show is that some people

15 respond more than others. So some people are likely to

16 experience something better than others. But what we

17 really don't know is whether this test will translate

18 to that effect.

19   And so the bottom line is that there will be

20 variability in the responding population; about that

21 there's no doubt. And how to translate this specific

22 response into that specific activity, frankly, I don't

 1 know. Perhaps Professor Casaburi would like to comment

 2 to this point.

 3   DR. CASABURI: You're absolutely right: no

 4 data is no data. So we really haven't studied whether

 5 a dose taken at 8:00 in the morning is going to

 6 translate into better exercise capacity at 4:00 in the

 7 afternoon when you want to run for that bus.

 8   On the other hand, because we've firmly

 9 linked the exercise capability benefit to improvements

10 in airflow, and we've demonstrated that the airflow

11 improvements persist from 10:00 in the morning --

12   MR. MULLINS: For how long?

13   DR. CASABURI: Well but we have data over the

14 time course of a day that looks very convincing, that

15 we see exercise tolerance -- I'm sorry, we see airflow

16 ability improve throughout the day and into the

17 evening, that it would be reasonable, in a physiologic

18 way, to assume that the exercise tolerance benefit

19 would persist as well. No data is no data, but a

20 reasonable assumption might be made.

21   DR. JACOBY: Okay, we're going to take a 10-

22 minute break now. We've had the three discussion

1 questions, we'll take a 10-minute break. We'll come

2 back at, let's make it an eight minute break. We'll

3 come back at 3:00 and we can have the three voting

4 questions at that point. Thank you. (A recess was

5 taken.) Questions to the Committee/Committee Discussion

6   (continued)

7   DR. JACOBY: We're missing a couple of

8 committee members here. You need to flash the lights

9 outside, start playing the overture to the second act.

10 I could go out in the hall.

11   Okay, now we have three voting questions

12 here. And for the voting questions, we use an

13 electronic voting system, so it's on your microphone

14 here. And once we begin the vote, the buttons start

15 flashing and they'll continue to flash even after

16 you've entered your vote. You press the button firmly

17 that corresponds to your vote. If you're unsure of

18 your vote, or you want to change it, you can press the

19 corresponding button until the vote is closed.

20   After everyone has completed their votes, the

21 vote will be locked in and the vote will then be

22 displayed on the screen here. So there's no secret

1 ballot here, everything's public. And the DFO will

2 then read the vote from the screen into the record.

3   Then we go around the room and each

4 individual who voted will state their name and their

5 vote into the record. And you can also state concisely

6 a reason why you voted as you did. And we'll continue

7 in that manner until all the questions have been

8 answered or discussed.

9   So the -- yes, Mr. Mullins?

10   MR. MULLINS: Yes sir, I have a question,

11 Chairman. This vote, the portion of the vote that is

12 made in regards to efficacy. Is it efficacy as far as

13 olodaterol 5 micrograms and also 10, or just 5?

14   DR. JACOBY: It's just for the one indicated,

15 the one dose that was indicated.

16   MR. MULLINS: Okay, I wanted to make sure

17 because there were a lot of assumptions back and forth.

18 I want to make sure, get clarification, all right.

19   DR. JACOBY: Right. Yes. Okay. So the

20 first question we're voting on, question four here, is

21 considering the totality of the data, has olodaterol

22 demonstrated substantial evidence of efficacy for the

300

1 long-term, once-daily maintenance treatment of airflow

2 obstruction in patients with chronic obstructive

3 pulmonary disease, or COPD, including chronic

4 bronchitis and/or emphysema?

5   And if not, what further data should be

6 obtained? So the question is not the if not part of

7 it, it's just whether efficacy has been demonstrated.

8 So vote on your microphones. Okay, has everyone voted?

9   UNIDENTIFIED SPEAKER: It's still flashing.

10   DR. JACOBY: Who hasn't voted? Okay. I

11 think that should be it.

12   DR. HONG: Okay, we have 15 yeses, and one no

13 and one abstain.

14   DR. JACOBY: Okay. So let's go around rather

15 than according to the order there. Dr. Hoidal?

16   DR. HOIDAL: Bronchodilators are a mainstay

17 of therapy for COPD. I think the sponsor's conducted a

18 rigorously designed trial, including background

19 therapy. I think there was significant sustained effect

20 as a bronchodilator was demonstrated.

21   I think it did well in head-to-head

22 comparisons with other established bronchodilators. It

1 has a favorable dosing schedule. And although the

2 symptomatic effects and treatment of symptoms were not

3 as great as hoped, it did have less rescue meds and

4 less dropouts.

5   DR. JACOBY: Thank you. I just need to

6 remind you, state your name and how you voted and then

7 a brief, concise explanation.

8   DR. HOIDAL: Sorry. John Hoidal, I voted

9 yes.

10   DR. JACOBY: Dr. Ameredes?

11   DR. AMEREDES: Bill Ameredes. I voted yes.

12 I agree with all the comments that Dr. Hoidal just

13 mentioned. And with reference to the including chronic

14 bronchitis and/or emphysema, based on the comments that

15 were made earlier, and the aspect that we were told by

16 the FDA that we are not voting for the safety part of

17 this, whether the drug is completely safe, we're also

18 not voting, in my opinion, whether this can be given to

19 every single patient. It can be tried in patients;

20 it's up to the physician.

21   DR. JACOBY: Dr. Carvalho?

22   DR. CARVALHO: Paula Carvalho. I voted yes.

1 I think that the sponsor did due diligence with finding

2 a dose response relationship. And I agree with the

3 comments of my predecessors here. The medication

4 should be given for obstructive, which I think is the

5 operative word, whether it's obstructive chronic

6 bronchitis and emphysema.

7   DR. JACOBY: Dr. Calhoun?

8   DR. CALHOUN: Calhoun, I voted yes for the

9 reasons previously stated. Just to amplify on the

10 point that Dr. Carvalho raised, which goes to Dr.

11 Terry's issue, the wording in the question is, once-

12 daily maintenance treatment of airflow obstruction.

13 It's not treatment of chronic bronchitis. It's not

14 treatment of emphysema. It's treatment of airways

15 obstruction in those diseases. And so I think so long

16 as the indication reflects that sense, that would be

17 great.

18   DR. JACOBY: Dr. Thadani?

19   DR. THADANI: I abstained for only one reason

20 because the question, there's no doubt the drug is

21 bronchodilator, but I would have loved to see some

22 outcome data. Because if I'm going to drug for life,

1 I'd love to see patients are not hospitalized for COPD

2 exacerbation, or they're not dying. For that reason,

3 it's the only reason I abstained.

4   And also I don't like the word emphysema in

5 there. I think if you could leave the word COPD that

6 would just suffice. Otherwise a lot of patients with

7 just pure emphysema is going to get the drug.

8   DR. JACOBY: Ms. Fiore?

9   MS. FIORE: Edna Fiore. I agree with the

10 previously stated reasons and vote yes. I would also

11 like to add that I can see an added attraction for this

12 medication. Because with a single dosage, or one a day

13 dosage, it would lead to better compliance. And also,

14 I know that some patients will skip doses for economic

15 reasons. And with the one-a-day dosage, that would be

16 overcome.

17   DR. JACOBY: Dr. Harkins?

18   DR. HARKINS: Michelle Harkins. I voted yes

19 for reasons mentioned. It did have an efficacy in a

20 real world setting, with other medications on board. I

21 agree a once-a-day is preferable to patients, myself

22 included.

1   DR. JACOBY: Dr. Connett?

2   DR. CONNETT: I voted yes on the narrowly

3 defined question of is it an effective bronchodilator?

4 I don't see that we have any evidence that it's

5 effective in preventing exacerbations, but that doesn't

6 seem to be the question that we're asked to address

7 here. And yeah.

8   DR. JACOBY: Dr. Blake?

9   DR. BLAKE: Kathryn Blake, and I voted yes.

10 I agree with the comments that have been made

11 previously, that it's an effective bronchodilator. And

12 one other feature that I think could contribute to its

13 effectiveness is the dosage format, which is I think an

14 improvement over the products that are currently out

15 there for COPD.

16   DR. JACOBY: David Jacoby. I voted yes. It

17 looks like a good bronchodilator to me. Dr. Terry?

18   DR. TERRY: I voted yes for the reasons Dr.

19 Calhoun and Dr. Carvalho mentioned.

20   DR. JACOBY: Dr. Greenberger?

21   DR. GREENBERGER: Paul Greenberger. I voted

22 yes. The two primary endpoints were achieved. And in

1 the 48-week studies, the endpoints were reached in the

2 setting of about 75 percent of the patients also

3 receiving LAMAs or SAMAs.

4   DR. JACOBY: Dr. Stone?

5   DR. STONE: Kelly Stone. I voted yes. The

6 data clearly demonstrated efficacy as a bronchodilator.

7   DR. JACOBY: Mr. Mullins?

8   MR. MULLINS: I voted -- stood alone on this

9 I guess, it looks like on a vote. And I guess my

10 thinking was through a prism of public health. And I

11 cannot I guess theoretically, and from a process

12 standpoint, support a trial and then support efficacy

13 in a trial that you know seemed to limit the

14 participants, or limits the participation of certain

15 populations and yet make assumptions on a broad-based

16 scale. So the efficacy is - - my question efficacy for

17 whom? And I think that when we say efficacy, we should

18 be able to say for the entire population. So that's

19 why I voted no.

20   DR. JACOBY: Dr. Tracy?

21   DR. TRACY: Jim Tracy and I voted yes. Most

22 of the reasons have already been mentioned, but just to

1 reiterate. Background medications, spectrum of disease

2 severity, real world setting, all the endpoints were

3 met.

4   DR. JACOBY: Dr. Herring?

5   DR. HERRING: I voted yes. The sponsor

6 showed significant evidence of efficacy as a

7 bronchodilator in multiple large, very well-designed,

8 real world clinical trials.

9   DR. JACOBY: And Dr. Brantly?

10   DR. BRANTLY: Dr. Brantly. I voted yes also,

11 for the same reasons as have been expressed.

12   DR. JACOBY: Great, thank you. The next

13 voting question is question five. Is the safety

14 profile of olodaterol adequate for approval for the

15 long-term, once- daily maintenance treatment of airflow

16 obstruction in patients with chronic obstructive

17 pulmonary disease, including chronic bronchitis and/or

18 emphysema? Go ahead and vote. Okay.

19   DR. HONG: We have 15 yeses, one no and one

20 abstain.

21   DR. JACOBY: Let's go around. Let's go in

22 the opposite direction this time. So Dr. Brantly?

1   DR. BRANTLY: I voted yes, because I believe

2 that the safety data shows no concerning safety signal.

3   DR. JACOBY: Dr. Herring?

4   DR. HERRING: Amy Herring. I voted yes. I

5 see no evidence based on these studies of any lack of

6 safety, with a caveat that of course we would need

7 careful post- market surveillance to prove safety.

8   DR. JACOBY: Dr. Tracy?

9   DR. TRACY: Jim Tracy. I too voted yes,

10 again urging post-marketing surveillance, especially in

11 the African-American population and with regard to

12 small cell disease.

13   DR. JACOBY: Mr. Mullins?

14   MR. MULLINS: I voted no on safety because

15 there are particular concerns I have with subsets of

16 the populations that don't exist in other populations

17 that should be considered. I cannot even consider

18 those endpoints in those various issues based on the

19 evidence that was presented by the sponsor.

20   And even though the sponsor, or those were

21 not considered of value, I think when you make a safety

22 assumption, safety is relative to the lifestyles,

1 structures and various biometrics and comorbidities

2 that we couldn't even consider based on the

3 presentation of the evidence.

4 And based on that premise, I don't think we

5 can make a total safety assumption based on the absence

6 of particular evidence for certain subpopulations.

7 DR. JACOBY: Dr. Stone?

8 DR. STONE: Kelly Stone. I voted yes. I

9 agree with the comments by Dr. Tracy. I think that the

10 safety was adequately demonstrated for approval.

11 DR. JACOBY: Dr. Greenberger?

12 DR. GREENBERGER: Paul Greenberger. I voted

13 yes. I thought the safety signals were looked for and

14 not found and the drug itself has one percent bio, oral

15 bioavailability, which is an advantage.

16 DR. JACOBY: Dr. Terry?

17 DR. TERRY: Peter Terry. I voted yes for the

18 reasons stated by Dr. Herring.

19 DR. JACOBY: David Jacoby. I voted yes. The

20 drug looked safe to me from the data that were

21 presented. Dr. Blake?

22 DR. BLAKE: Kathryn Blake. I voted yes. I

1 didn't see any safety issues that were of concern and I

2 felt that they were adequately addressed.

3   DR. JACOBY: Dr. Connett?

4   DR. CONNETT: This is John Connett. I voted

5 yes. And I don't have significant reservations

6 regarding safety.

7   DR. JACOBY: Dr. Harkins?

8   DR. HARKINS: Michelle Harkins. I also voted

9 yes. I think this is on par with most LABA studies and

10 I didn't see any safety concerns.

11   DR. JACOBY: Ms. Fiore?

12   MS FIORE: Edna Fiore. And I voted yes, in

13 agreement with the previous stated opinions.

14   DR. JACOBY: Dr. Thadani?

15   DR. THADANI: I had to abstain since I

16 abstained from the last question or I'd be

17 contradicting myself. I have no safety issues per se

18 with the drug.

19   DR. JACOBY: Dr. Calhoun?

20   DR. CALHOUN: Bill Calhoun. I voted yes for

21 the reasons stated. I think that it is probably

22 warranted to keep an eye out on the small cell signal.

1 That may be nothing, but it's enough to just warrant

2 some careful consideration.

3   DR. JACOBY: Dr. Carvalho?

4   DR. CARVALHO: I voted yes for the reasons

5 previously stated and would also urge post-marketing

6 surveillance.

7   DR. JACOBY: Dr. Ameredes?

8   DR. AMEREDES: Bill Ameredes. I voted yes.

9 I do have a small concern, as Dr. Calhoun mentioned,

10 about the neoplasms, but the safety was comparable to

11 other drugs. And again I'm keeping in mind that the

12 text of this question stresses the word adequate and

13 not that we are voting if the drug is completely safe.

14   DR. JACOBY: And Dr. Hoidal?

15   DR. HOIDAL: John Hoidal. I voted yes for

16 the reasons stated, and also concur with the

17 recommendations made.

18   DR. JACOBY: Thank you. The final question,

19 question six, based on the information included in the

20 briefing materials and presentations, has the applicant

21 provided sufficient efficacy and safety data to support

22 marketing of olodaterol inhalation solution for the

1 long- term, once-daily maintenance treatment of airflow

2 obstruction in patients with chronic obstructive

3 pulmonary disease, including chronic bronchitis and/or

4 emphysema? Go ahead and vote. Okay.

5   DR. HONG: We have 15 yeses, one no and one

6 abstain.

7   DR. JACOBY: Dr. Hoidal?

8   DR. HOIDAL: John Hoidal. I voted yes. I

9 think we've discussed the efficacy and safety.

10   DR. JACOBY: Dr. Ameredes?

11   DR. AMEREDES: Bill Ameredes. I voted yes.

12 I do believe that they did this, I think it was a great

13 thing that they did. It's the best that we have right

14 now and perhaps it's going to push us to consider this

15 in a much more comprehensive fashion in the future.

16   DR. JACOBY: Dr. Carvalho?

17   DR. CARVALHO: Paula Carvalho. I also voted

18 yes, although I would make a caveat regarding the

19 exercise response as being sustained versus not.

20   DR. JACOBY: Dr. Calhoun?

21   DR. CALHOUN: Bill Calhoun. I voted yes with

22 demonstrated efficacy and demonstrated safety.

1   DR. JACOBY: Dr. Thadani?

2   DR. THADANI: I had to abstain since I

3 abstained from the other two. I would have -- I think

4 it's a great -- there's no doubt as a bronchodilator.

5 I would still emphasize that I'd really like to see

6 some hard outcome data because a patient will be on

7 this treatment for life. I would like him to be less

8 hospitalized and other issues, and that's the reason I

9 abstained.

10   DR. JACOBY: Ms. Fiore?

11   MS. FIORE: Edna Fiore. I voted yes and I

12 will be anxiously awaiting the availability of this

13 product.

14   DR. JACOBY: Dr. Harkins?

15   DR. HARKINS: Michelle Harkins. I voted yes

16 for previous stated reasons.

17   DR. JACOBY: Dr. Connett?

18   DR. CONNETT: This is John Connett. I voted

19 yes, assuming that they don't employ in their package

20 insert the information that we saw on exercise.

21   DR. JACOBY: Dr. Blake?

22   DR. BLAKE: Kathryn Blake. I voted yes for

1 the reasons as stated for the first two questions.

2   DR. JACOBY: David Jacoby. I voted yes for

3 the reasons I've already stated. Dr. Terry?

4   DR. TERRY: Peter Terry. I voted yes for the

5 same reasons as I voted yes for four and five.

6   DR. JACOBY: Dr. Greenberger?

7   DR. GREENBERGER: Paul Greenberger, yes. I

8 voted yes for the reasons for questions four and five.

9   DR. JACOBY: Dr. Stone?

10   DR. STONE: Kelly Stone. I voted yes, both

11 safety and efficacy were adequately demonstrated.

12   DR. JACOBY: Mr. Mullins?

13   MR. MULLINS: I voted no because of the

14 length of the trial and also for sustainability. I

15 think that a lay person might make false assumptions

16 about the capabilities, the additional capabilities of

17 the drug based on how the trial was conducted.

18   DR. JACOBY: Dr. Tracy?

19   DR. TRACY: Jim Tracy. I voted yes for the

20 previously stated reasons.

21   DR. JACOBY: Dr. Herring?

22   DR. HERRING: Amy Herring. I voted yes for

1 the previously stated reasons.

2   DR. JACOBY: And Dr. Brantly?

3   DR. BRANTLY: Mark Brantly. I voted yes for

4 the previously stated reasons.

5   DR. JACOBY: Okay. Thank you. Don't leave.

6 Dr. Michele has some final comments to make. But I'd

7 like to thank everyone on all sides of the table here

8 for your participation today.

9   DR. MICHELE: Well thank you. This was

10 certainly a very interesting conversation. We have our

11 work cut out for us. And you've given us a great deal

12 of food for thought, and I suspect something that will

13 need to be taken forward for further discussion.

14   So with that, I'd just again like to thank

15 everyone. Thank you to Boehringer Ingelheim for their

16 presentations. And especially thank you to our

17 audience members and the committee for being here. We

18 very much appreciate your input.

19   (Whereupon, at 3:21 p.m., the Meeting of the

20   Pulmonary-Allergy Drugs Advisory Committee

21   was adjourned.)

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